Neurology

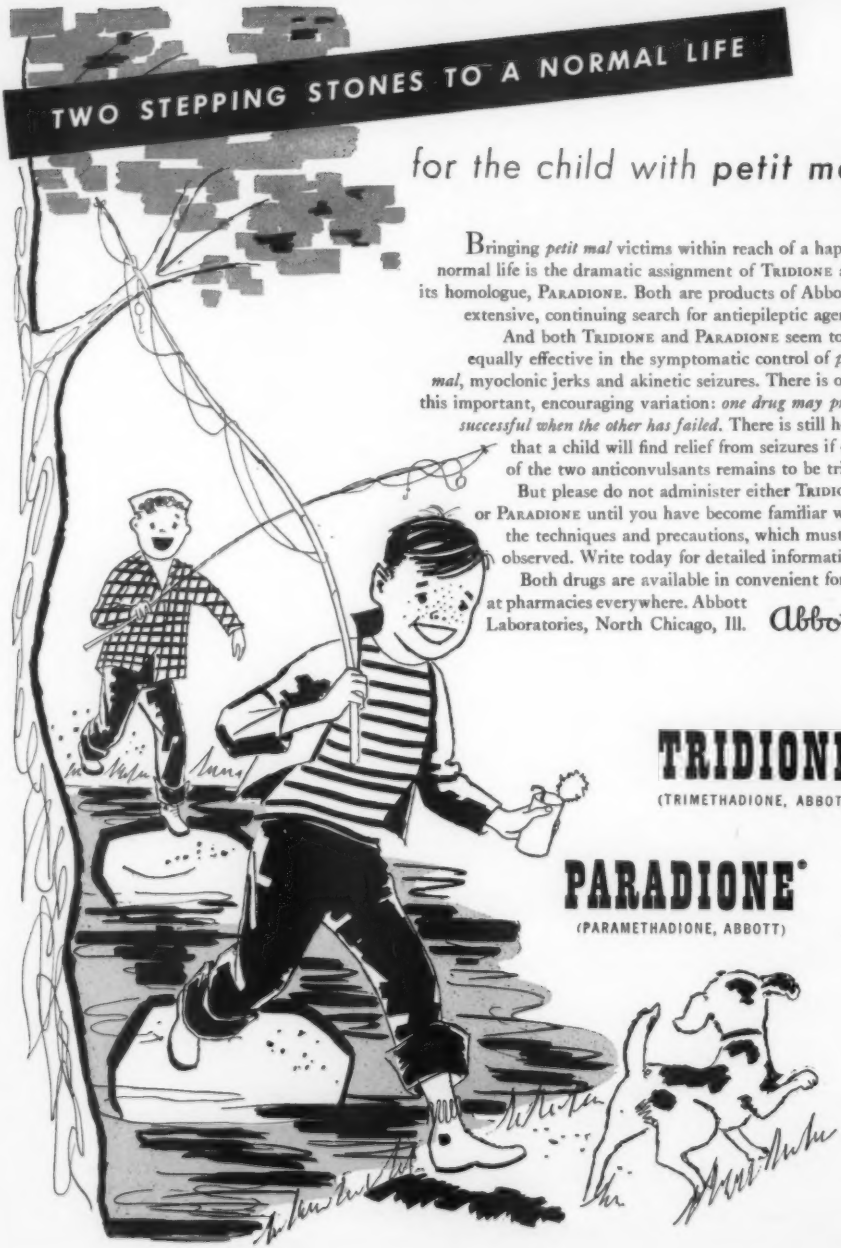
OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

SEPTEMBER-OCTOBER · 1951
Volume 1 · Number 5

TWO STEPPING STONES TO A NORMAL LIFE

for the child with **petit mal**

Bringing *petit mal* victims within reach of a happy, normal life is the dramatic assignment of TRIDIONE and its homologue, PARADIONE. Both are products of Abbott's extensive, continuing search for antiepileptic agents. And both TRIDIONE and PARADIONE seem to be equally effective in the symptomatic control of *petit mal*, myoclonic jerks and akinetic seizures. There is only this important, encouraging variation: *one drug may prove successful when the other has failed.* There is still hope that a child will find relief from seizures if one of the two anticonvulsants remains to be tried. But please do not administer either TRIDIONE or PARADIONE until you have become familiar with the techniques and precautions, which must be observed. Write today for detailed information. Both drugs are available in convenient forms at pharmacies everywhere. Abbott Laboratories, North Chicago, Ill. Abbott



TRIDIONE®
(TRIMETHADIONE, ABBOTT)

PARADIONE®
(PARAMETHADIONE, ABBOTT)

"Dramatic" IN THE PROMPT RELIEF OF POSTERIOR NERVE ROOT PAIN OF HERPES ZOSTER

PROTAMIDE★

(SHERMAN)

Gratifying clinical results have been obtained with the use of Protamide (Sherman) in the treatment of the extremely resistant herpes syndrome. Pain relieved in the great majority of cases within four to forty-eight hours and lesions healed in ten days or less—regardless of the particular nerve roots involved.

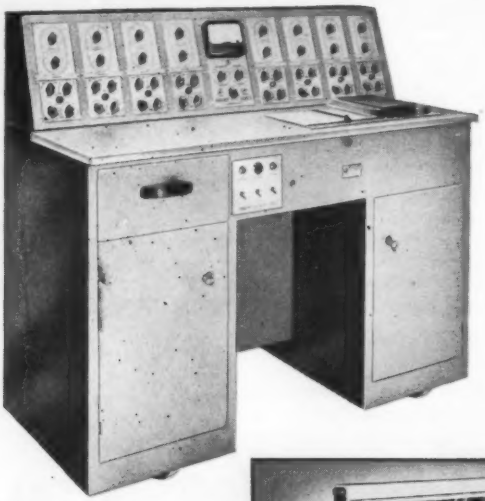
Protamide is a sterile, aqueous, colloidal solution of a specially processed proteolytic enzyme . . . clinically proved for the maximum relief of nerve root pains of Herpes Zoster and Tabes Dorsalis.

All Protamide is clinically tested for positive results. Can be stored at room temperature without loss of potency. Write for new literature and a recent reprint on Protamide for Tabes Dorsalis.

★CLINICALLY PROVED. Several papers already presented and more being prepared on this and other therapeutic uses. U. S. Armed Forces Med. Journal, Sept. 1950 (Marsh, Wm. C.) Urol. and Cutan. Rev. May 1947 (Costello, R. T.) Ohio State Med. Journal, January 1951 (Lehrer; Henry W.; Lehrer; David R.; Lehrer, H. G.) Urol. and Cutan. Rev., Aug. 1944 (Lehman A. J.; Chase, H. F.; Yonkman, F. F.)

SHERMAN LABORATORIES
G. H. Sherman, M. D., Founder
BIOLOGICALS • PHARMACEUTICALS
DETROIT 15, MICHIGAN

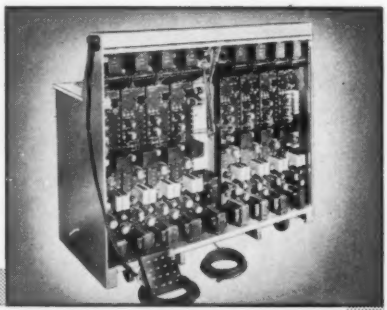
MODERN NEUROLOGY
requires dependable diagnosis



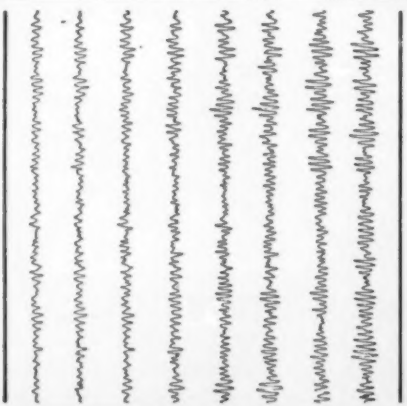
MEDCRAFT Model D
Electroencephalograph

Requires no shielded rooms
All components plug into position
No B batteries

Write for specifications and prices



REAR VIEW — Showing accessibility of components



Representatives in principal cities

MEDCRAFT ELECTRONIC CORP.
41-41 Twenty-fourth Street
Long Island City 1, N. Y.
Stillwell 6-5584

Sales & Service

Boston Baltimore Chicago New Orleans
Pittsburgh Birmingham San Francisco San Antonio

Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

BOARD OF EDITORS

Editor-in-Chief: RUSSELL N. DEJONG, M.D.
Ann Arbor, Michigan

Associate Editor: WEBB HAYMAKER, M.D.
Washington, D.C.

Editorial Board:

RAYMOND D. ADAMS, M.D., *Boston, Massachusetts*

PEARCE BAILEY, M.D., *Washington, D.C.*

FRANCIS M. FORSTER, M.D., *Washington, D.C.*

PAUL F. A. HOEFER, M.D., *New York, New York*

MABEL G. MASTEN, M.D., *Madison, Wisconsin*

RICHARD B. RICHTER, M.D., *Chicago, Illinois*

ALPHONSE R. VONDERAHE, M.D., *Cincinnati, Ohio*

A. EARL WALKER, M.D., *Baltimore, Maryland*

ROBERT WARTENBERG, M.D., *San Francisco, California*

PAUL I. YAKOVLEV, M.D., *Middletown, Connecticut*

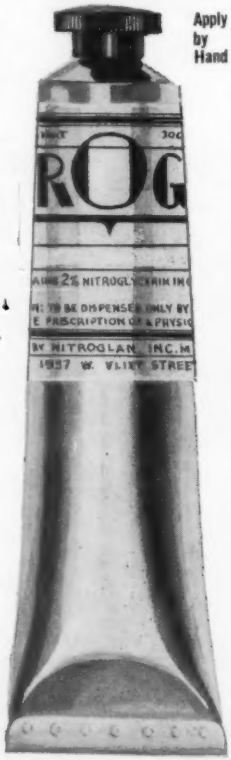
NEUROLOGY, copyright 1951 by Lancet Publications, Incorporated. Title registered United States Patent Office.

Entered as second class matter at the post office at Minneapolis, Minnesota, January 23, 1951.

NITROGLAN INC.

A 2% nitroglycerine* ointment with a lanolin† base. Indicated for Raynaud's Disease, frostbite and peripheral-vascular disturbances as well as where there are trophic skin changes.

Nov. 22, 1950 Proceedings of the Staff Meetings of the Mayo Clinic show a 66⅔% positive effect in Raynaud's Disease (which is much greater and more important than the usual 50% achieved in surgical sympathectomy).



In 30-gram sealed tubes only

● Dr. Max J. Fox of Milwaukee, whose paper in the Wisconsin Medical Journal (reviewed in Journal of the A. M. A.) emphasizes that before surgery is attempted, NITROGLAN always should be tried, whether in Raynaud's or Buerger's diseases, says: "No other medication has given the encouraging results shown by applying NITROGLAN to Raynaud's cases and Raynaud-like cases."

This local treatment requires no laboratory control. The schedule is simple and application easy and the side effects are easily tolerated. Dose is one-half inch ribbon squeezed from tube. To be sure your patient gets 2% Nitroglycerin in Lanolin, prescribe NITROGLAN.

*Lion †Lamb

Write for literature to

NITROGLAN, INC. • 1937 W. VLIET STREET MILWAUKEE 5, WISC.

Internationally Endorsed by Psychiatrists

REITER ELECTROSTIMULATORS

THE ORIGINAL THERAPEUTIC CEREBRAL STIMULATORS

The Reiter Electrostimulators provide therapeutic effect by means of specific LOW CURRENTS.

●

MODEL CW46J
for entire range of convulsive therapy

Using unidirectional currents, the Reiter Electrostimulators have been developed to produce a soft, smooth-appearing and feeling convulsion with from 3 to 20 milliamperes as required by the individual patient. All undesirable side effects of the convulsion are greatly minimized, avoiding memory defect, physical thrust, apnea, etc. A single attendant is adequate.

OTHER MODELS

MODEL CW47
for nonconvulsive prolonged stimulative therapy
for combined convulsive therapy and stimulative therapy
for stimulative therapy and respiratory problems as in barbiturate coma

MODEL RC47
for prolonged deep coma therapy

MODEL VA47
for stimulative therapy and respiratory problems as in barbiturate coma
(Designed specially for General Hospital respiratory problems)

ALL MODELS EQUIPPED WITH SPECIAL ELECTRODES WHICH REQUIRE NO JELLY

Each model housed in a handsome, portable walnut cabinet which is reasonably lightweight. Operated from ordinary house current of 115 volts AC. Each model fully supplied with appropriate electrodes.

●

Write Dept. N for Descriptive Literature.

REUBEN REITER, Sc. D.

38 WEST 48th STREET, ROOM 606, NEW YORK 19, N. Y.

WHEN FLACCID MUSCLES ARE AN ASSET

'SYNCURINE' brand

DECAMETHONIUM BROMIDE (C 10) INJECTION

'Syncurine' is a NEW skeletal muscle relaxant with practical advantages in surgery and during electric shock therapy.

'SYNCURINE' does not induce spasm of the bronchi or larynx because it does not release histamine-like substances . . . absence of such spasm eliminates a common hindrance to endotracheal intubation.

'SYNCURINE' effect is more easily controlled than that of curare derivatives because it is rapidly eliminated. The timing of its action is such that it may be used to facilitate peritoneal closing "with the assurance that adequate spontaneous respiration will be present by the time the operation has been completed."[1]

DOSAGE: *Detailed information as to dosage will be sent on request, or it can be obtained from the package circular.*

PRECAUTIONS: *'Syncurine' administration requires the skillful judgment of the trained anesthetist. In case of respiratory depression from overdosage, controlled or artificial respiration is essential and adequate.*

PACKAGING: *'Syncurine' brand Decamethonium Bromide (C 10) Injection 10 cc. rubber-capped vials containing 1 mg. per cc.*

REFERENCES:

(1) Organe, G.: Lancet, 1:773, 1949.
(2) Grab, D., Holaday, D. A. and Harvey, A. McG.: New Eng. J. Med. 241:812 and 816, 1949.
(3) Castillo, J. C., and de Beer, E. J.: Fed. Proc. Part 1 8:279, 1949.
(4) Castillo, J. C., Phillips, A. P. and de Beer, E. J.: J. Pharm. and Exp. Ther. 97:150, 1949.
(5) Spencer, C. H. and Coakley, C. S.: Med. Ann. Dist. Col. 19:132, 1950.
(6) Harris, L. C. and Dripps, R. D.: J. Anesthesiology 11:214, 1950.

BURROUGHS WELLCOME & CO. (U.S.A.) INC. Tuckahoe 7, New York

GRASS INSTRUMENT CO.

101 OLD COLONY AVE.
QUINCY, MASS.
PR3-0002

SPECIFY
A GRASS MODEL III SERIES ELECTROENCEPHALOGRAPH

THE INSTRUMENT PROVEN BY
THE MOST FAMOUS HOSPITALS, UNIVERSITIES, AND CLINICS
THROUGHOUT THE WORLD
FOR
ACCURACY
DEPENDABILITY
ECONOMY
CONVENIENCE
EXPANDABILITY

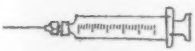
ACCEPTED — COUNCIL ON PHYSICAL MEDICINE and REHABILITATION — AMERICAN MEDICAL ASSOCIATION

LISTED UNDER RE-EXAMINATION SERVICE — UL — UNDERWRITERS' LABORATORIES, INC.

MAKERS OF ELECTROENCEPHALOGRAPHS AND
ELECTROPHYSIOLOGICAL INSTRUMENTS SINCE 1935

For the Common Anemias...

The Squibb RUBRA Family

	RUBRAMIN *per cc.*	RUBRAFOLIN *per capsule*	RUBRATON *per teaspoonful*	RUBRAFERATE *per capsule*
				
VITAMIN B_{12}	**15, 30 & 50** micrograms	**25** micrograms	**4.17** micrograms	**4.17** micrograms
FOLIC ACID		**1.67** milligrams	**0.28** milligrams	**0.28** milligrams
IRON			**220** milligrams ferric ammonium citrate	**130** milligrams ferrous sulfate exsic.
VITAMIN C				**50** milligrams
DOSAGE THERAPEUTIC	15 to 30 micrograms daily for a week or more; when neurologic involvement is present, 50 micrograms or more daily.	1 or 2 capsules daily	2 teaspoonfuls t.i.d.	2 capsules t.i.d.
MAINTENANCE	Generally, 30 to 50 micrograms twice a month; when neurologic involvement is present, 50 micrograms a week.	1 capsule daily	1 teaspoonful t.i.d.	1 capsule t.i.d.
SUPPLY	1 cc. ampuls, 15 & 30 micrograms of vitamin B_{12} per ampul. 5 & 10 cc. vials, 30 micrograms per cc. 10 cc. vials 50 micrograms per cc.	Bottles of 100	Pint and gallon bottles	Bottles of 100

NOTE: The above are average doses. As with all antianemia preparations, dosages must be adjusted to meet the needs of the individual patient.

Also available: Solution Rubramin Crystalline (Squibb Crystalline Vitamin B_{12} Solution) in 1 cc. ampuls, 15 micrograms of crystalline vitamin B_{12} per ampul, and 10 cc. vials, 30 micrograms of crystalline vitamin B_{12} per cc.

"RUBRAMIN" IS A REGISTERED TRADEMARK AND "RUBRAFOLIN", "RUBRATON" AND "RUBRAFERATE" ARE TRADEMARKS OF E. R. SQUIBB & SONS

Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

Volume 1, Number 5

Contents • SEPTEMBER-OCTOBER, 1951

The Human Frontocorticopontine Tract: Functional Inconsequence of its Surgical Interruption
RUSSELL MEYERS, M.D. 341

Phenomena and Correlates of the Psychomotor Triad
WILLIAM G. LENNOX, M.D. 357

Intracranial Neoplasm Associated with Fourteen and Six Per Second Positive Spikes
WAYLAND A. STEPHENSON, M.D. 372

Anticonvulsant and Toxic Effects of Alpha-Phenyl-Butyrylurea
MARSHALL J. ORLOFF, M.D., P. E. FELDMAN, M.D., CHARLES H. SHAIOVA, M.D. AND CARL C. PFEIFFER, PH.D., M.D. 377

Extradural Hematoma of the Posterior Fossa
RICHARD C. SCHNEIDER, M.D., EDGAR A. KAHN, M.D. AND ELIZABETH CAROLINE CROSBY, PH.D., SC.D. 386

(Continued on next page)

NEUROLOGY is published bimonthly at Minneapolis. Publication dates: January, March, May, July, September, November. Subscription rate: $8.00 a year, $1.50 a copy; outside U.S., $9.00 a year, $1.70 a copy. Louis M. Cohen, Publisher. Margaret M. Kane, Managing Editor. Maurice Wolff, Business Manager. NEUROLOGY, 84 South Tenth Street, Minneapolis 3, Minnesota.

ADVERTISING REPRESENTATIVES. NEW YORK 17: George Doyle, Lee Klemmer, Bernard A. Smiler, John Winter, 50 East 42nd Street. Telephone: Murray Hill 2-8717. CHICAGO 6: Jay H. Herz, 20 North Wacker Drive, Suite 1921. Telephone: Central 6-4819. SAN FRANCISCO 4: Duncan A. Scott & Co., Mills Building. Telephone: Garfield 1-7950. LOS ANGELES 5: Duncan A. Scott & Co., 2978 Wilshire Boulevard. Telephone: Dunkirk 8-4151.

THE NEW *Edin* ink-writing ELECTROENCEPHALOGRAPH

METAL CONSOLE—MOBILE
CONTROLS WITHIN REACH
OF SEATED OPERATOR

- IMPROVED DESIGN — The model 400A series incorporates the latest developments and engineering improvements in electroencephalographic recorders.
- COMPLETELY A.C. OPERATED (115 Volt, 60 Cycles, Special voltage and frequency circuits available on order). No A or B batteries to replace or charge.
- HIGH IN-PHASE REJECTION RATIO (10,000 to 1 guaranteed). Less interference from other potentials originating outside the electrode zone.
- EXTENDED FREQUENCY RESPONSE (up to 200 cps.). Provides truer EEG records and is especially suited for EMG tracings.
- INTERCHANGEABLE MAIN and PRE-AMPLIFIER. Provides simplified and easy servicing if required. All units are electrically connected by plugs.
- NO SHIELDING NORMALLY REQUIRED. Capacitive electrical interference is completely rejected without loss of high frequency response. Instrument is mobile and may be used in various locations of an installation.

Write factory for further details

EDIN COMPANY INC. Worcester 8, Mass., U. S. A.

Contents—*Continued*

Treatment Review

The Treatment of Purulent Meningitis

A. L. SAHS, M.D. 394

Clinical Pathologic Conference

PRESENTED BY BEN W. LICHTENSTEIN, M.D. 410

Book Reviews

Spiegel's *Progress in Neurology and Psychiatry* 417

Reeves' *Cranioplasty* 417

Cass' *Speech Habilitation in Cerebral Palsy* 418

INFORMATION FOR *Authors*

NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

Manuscripts of papers read at meetings of the Academy must be filed with the secretary at the time of the meeting, and will be published if acceptable to the editorial board. They are the property of the Academy, and authors who wish to publish them elsewhere must first request release.

Manuscripts submitted for publication (other than those read at meetings of the Academy) should be sent to Dr. Russell N. DeJong, University Hospital, Ann Arbor, Michigan. Books for review and business correspondence should be addressed to NEUROLOGY, 84 South Tenth Street, Minneapolis 3, Minnesota. Articles dealing with the history of neurology should be sent to Dr. Webb Haymaker, Armed Forces Institute of Pathology, 7th and Independence, S. W., Washington 25, D. C. News items related to the American Academy of Neurology or to the field of neurology in general are to be sent to Dr. Pearce Bailey, 4725 Sedgwick, N. W., Washington 16, D. C.

Manuscripts are accepted for publication on condition that they are contributed solely to NEUROLOGY. They must be typewritten, double spaced, and only the original copy should be submitted. Illustrations should be drawn in India ink on white paper with clear lettering. Photographs should be glossy prints. Tables should be typed on separate sheets. The title of the article, name of author and number of figure should be placed on the back of every illustration, and the top should be designated. Legends for figures should be typed and are not to be attached to the illustrations. If the number of illustrations or tables is excessive, the author will be asked to defray a part of the cost.

References should be designated in the text by superior number, and should be listed at the end of the article in numerical sequence. They should be typed in the following manner:

Journal reference: 1. Franklin, C. R., and Brickner, R. M.: Vasopasm associated with multiple sclerosis, Arch. Neurol. & Psychiat. 58:125, 1947.

Textbook reference: 2. Wechsler, I. S.: A Textbook of Clinical Neurology, ed. 3, Philadelphia, W. B. Saunders Company, 1935, pp. 194-199.

Abbreviations should follow the style of the Quarterly Cumulative Index Medicus.

Galley proofs will be sent to authors for prompt correction. There will be no charge for corrections unless excessive alterations are made. A schedule of charges for reprints will accompany the galley proof.

sleep . . . ***measured by the patient's need***

Palatable Elixir Alurate, with its flexible, easily adjusted dosage, enables you to induce sleep in nervous, tense patients according to their individual needs. In therapeutic doses, it does not alter heart rate, respiration or other vital functions. In most cases, sleep of normal duration and depth is obtained. Easily administered, pleasant-tasting, freely miscible with liquids, each teaspoonful of Elixir Alurate contains ½ gr of allyl-isopropyl barbituric acid. Bottles of 6 oz, 1 pt, and 1 gal.

HOFFMANN-LA ROCHE INC. • NUTLEY 10 • N. J.

Elixir Alurate®

'Roche'

Neurology

The Human Frontocorticopontine Tract: Functional Inconsequence of Its Surgical Interruption

Russell Meyers, M.D.

WHILE a measure of disagreement still exists regarding certain refinements of the frontocorticopontine pathway (frontopontine tract, Arnold's bundle*), most writers appear to agree that the tract constitutes a recognizable component of the extrapyramidal system; that it arises from the infragranular layers, V and VI, of the frontal cortex;[13, 20] passes through the anterior limb of the internal capsule commingled with or posterior to the thalamofrontal and frontothalamic fibers, but in either case anterior to the genu of the capsule; converges upon the ipsilateral crus cerebri and is there distributed in the medial portion of the peduncle; and terminates for the most part in the ipsilateral rostrodorsal (pretrigeminal) pontine nuclei,[14, 17, 30, 32, 35] establishing synapses with pontocerebellar neurons.

Anatomic, pathologic and electrophysiologic studies abundantly support the view that, by means of pontocerebellar fibers travelling in the brachium pontis, the corticopontine impulses are distributed to (a) the neocerebellar cortex (anisform and paramedian lobes), chiefly contralaterally but to a small extent ipsilaterally;[3, 4, 6, 7, 14, 20, 36] (b) the whole

*This bundle should be clearly distinguished from the temporothalamic tract to which Arnold's name is also attached. The latter is not under consideration in the present article.

From the division of neurosurgery, State University of Iowa Hospitals, Iowa City, Iowa.
Presented with motion picture illustrations at the thirty-sixth annual congress of the American College of Surgeons, Forum on Fundamental Surgical Problems, Boston, Massachusetts, October 25, 1950.

of the vermis (excepting the nodulus) bilaterally;[7, 8, 11, 32] and (c) the paraflocculus.[11]

There appears to be considerably less accord concerning the "function(s)" of the frontocorticopontine tract. In 1914, Weed,[37] employing cats, reported that damage to one frontocorticopontine tract, whether in the cortex, internal capsule or peduncle, results in homolateral rigidity. Stimulation of the injured site effectively inhibited this rigidity unless the middle or superior cerebellar peduncles were previously severed. Weed's findings were largely confirmed in 1923 by Warner and Olmsted,[36] the major point of dissension between them being over the side affected by destruction of a frontocorticopontine tract. Warner and Olmsted contended that the limbs most severely afflicted are those contralateral to the lesion.

Elliot Smith,[31] speaking of the prefrontal area of the human brain, asserted, "When this area or the fiber tract arising from it is thrown out of action, the restraint is removed from the complicated muscular mechanisms that automatically maintain the posture of the body: hence the limbs tend to become rigid in a position of extension. Alternatively under normal conditions . . . it releases the fixed posture so that the muscles can obey the impulses determining skilled action." Smith held that this function was accomplished in collaboration with the cerebellum.

In consequence of extensive inquiries in comparative neurology, Abbie[1] concluded, "With a frontal cortex appears a fronto-pontine pathway and it is known that this exists in all mammals used for experimental purposes for they develop decerebrate rigidity when it is interrupted." Supporting his thesis by reference to Wilson's[38] clinicopathologic findings on decerebrate states in man, Abbie concluded, "there can be no doubt that the same (frontocorticopontine) mechanism is affected" and that injury to this pathway "is sufficient to produce a complete manifestation of rigidity without the intervention of the temporo-pontine system." Like Smith, he declared, "The function of the fronto-pontine pathway appears to be the release of the muscles from the economical rigidity of the standing posture immediately the will decides to alter that posture."

More recent writers, though not directly contravening the views of Weed, Smith and Abbie, have seldom alluded to the role of the frontocorticopontine tract in inhibiting postural rigidity. Papez, Bennett and Cash,[27] for example, ventured the opinion that the functions of the frontopontocerebellar pathway are to collaborate with the corticospinomuscular pathways for the "release, patterning and energizing of movement." In 1942, Mettler[20] advanced a circuit-feed-back account, proposing that "the cortex energizes the cerebellum through the corticopontine circuit but

inhibits through the striatal circuit the specific sublobules (of the cerebellum) dealing with the muscle groups antagonistic to the movements in progress. . . . The cerebellum, corticopontal and striatal tracts may thus be looked upon as responsible for a high type of reciprocal innervation of opposing groups of skeletal muscles."

Kuntz[14] asserted simply that "unilateral synergia of the extremities involves the activation of the cells of Purkinje by impulses conducted through the cortico-ponto-cerebellar conduction pathway" and Buchanan,[9] even less committal, observed that the corticopontile fibers "function in the coordination of voluntary muscles throughout the body."

In his 1950 *Essays on the Cerebral Cortex*, Von Bonin[35] proposed that by means of the corticopontine fibers, the cortex "sets the servomechanism" (i.e., the cerebellum, and the rubroolivodentate and pallidonigral systems) so that it supports the "steering" of the final common pathway by the pyramidal system.

That the demonstration of a "function" properly attributable to any particular corticofugal-cerebellar fibers might not prove as feasible as many writers have supposed was suggested by Bailey[3] in 1949. "Anatomical connections," he said, "are sufficiently complex in the central nervous system to make it obvious that no part of it performs any function independent of, and isolated from, many other parts. Functions are not localized in specific parts of the system, but all are parts of a functioning whole."

THE PROBLEM

The role of the frontocorticopontine tract in man is as yet obscurely understood. Much of what has been claimed for the human up to now has been reached by inference from animal experimentation rather than from crucial observations in man himself. In brief summary, the claims include (a) the inhibition of decerebrate rigidity;[1, 36, 37] (b) the release of fixed postural motor "set" so that the muscles can obey voluntary impulses determining skilled acts;[1, 31] (c) the release, patterning and energizing of movement;[27] (d) "high-type" reciprocal innervation of skeletal muscles;[20] (e) synergia of the extremities;[14] (f) coordination of voluntary muscles throughout the body;[9] and (g) "setting" of the servomechanism so that the pyramidal impulses may properly "steer" the final common pathway.[35]

Some of these claims[1, 6, 36] expressly indicate that damage to the frontocorticopontine tract results in manifest motor disabilities; others do so by implication. The issue arises, therefore, whether any or all of them can be supported by data derived directly from human subjects.

MATERIAL AND METHODS

The subjects of the present study consist of 23 adult males and females who exhibited motor disorders commonly termed "extrapyramidal" diseases. Twenty-two presented the clinical picture of parkinsonism of postencephalitic or idiopathic origin. Cases of apparently arteriosclerotic origin were excluded. The twenty-third patient, a female, suffered from oculogyric crises and severe dystonia of the muscles of the tongue and lower jaw. The disorder in this case was probably of postencephalitic origin.

The parkinsonian patients were part of a larger series of 38 cases of unilateral and bilateral parkinsonism who, during a ten year period beginning March 7, 1939, had been subjected to surgery at the level of the basal ganglia in the endeavor to ameliorate their abnormal motor phenomena.* Their ages ranged from 23 to 56 years, the majority being in the fourth decade. Twenty-two of these, having been subjected, among other surgical procedures, to section of the anterior limb of the internal capsule including that portion generally supposed to transmit the fronto-corticopontine tract, were considered pertinent to the present inquiry.

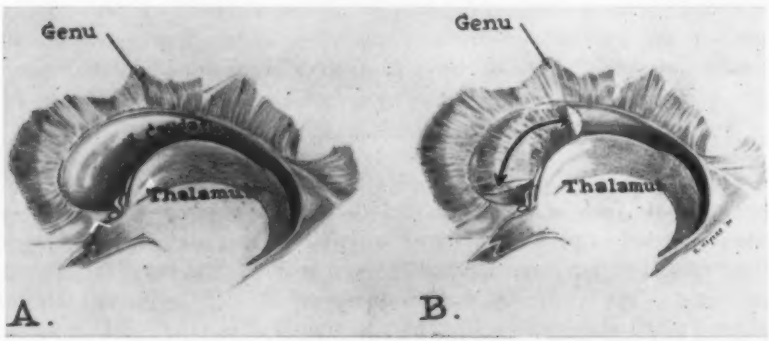


FIG. 1. Sketches to illustrate approximate line of incision through anterior limb of internal capsule employed in parkinsonian patients. A. Before removal of head of caudate nucleus. B. After removal of caudate head, exposing mesial aspect of anterior capsular limb.

The line of surgical section of the anterior limb carried out in these cases is illustrated diagrammatically in figure 1 and anatomico-pathologically in figure 2.

*The data derived from these cases together with those of smaller series of patients exhibiting choreo-athetosis, hemiballismus and spasmodic torticollis have been made the subject of a separate report.[25]

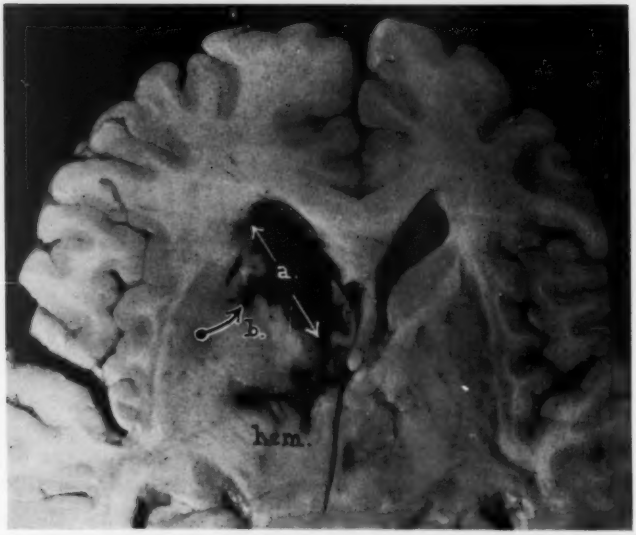


FIG. 2. Horizontal section of brain of patient A.L., a 39 year old housewife with generalized rigidity and severe alternating tremors of the right side. Planned operative procedure: extirpation of left caudate head and section of anterior limb of left internal capsule. Death on third postoperative day. (a) illustrates ablation of left caudate head and (b), that segment of the curvilinear incision through the anterior limb fibers which crosses this particular horizontal level (arrow). In addition, an unintended hemorrhagic extravasation into the genu, thalamus and posterior pole of the globus pallidus is visible (hem). The latter probably represents the fatal lesion.

Further details concerning the surgical measures employed in the parkinsonian subjects are summarized in table 1. Three patients died within a few days of operation. One of these had been subjected to extirpation of the caudate head and section of the anterior limb of the internal capsule; another, to extirpation of the caudate head, section of the anterior limb and extirpation of the oral portion of the putamen; and the third, to extirpation of the caudate head and section of both the anterior limb and pallidofugal fibers.[23, 24] In addition, five patients remained unimproved by operation. Because of the persistence of pre-existing disabilities of the limbs the latter were not considered critically useful cases for the present study. This left a total of 14 parkinsonian patients in whom the frontocorticopontine tract had presumably been interrupted and whose motor power and status, deep and superficial reflexes, praxis, equilibratory and non-equilibratory coordination and cutaneous and proprioceptive sensory functions could be reliably evaluated both pre- and postoperatively.

TABLE 1

SUMMARY OF SURGICAL MEASURES EMPLOYED IN 22 CASES OF PARKINSONISM

Surgical Procedure	*Number of Cases*
Ch, Ac	8
Ch, Ac, Pt	4
Ch, Ac, Pt, Gl	2
Pfs, Ch, Ac	6
Pfs, Ch, Ac, Pt	1
Ch (Rt); Ch, Ac, PrU, (Lt)	1
	22*

LEGEND: Ch = extirpation of head of caudate nucleus; Ac = section of anterior limb of internal capsule as far posteriorly as the genu of the internal capsule; Pt = extirpation of oral ⅓ to ½ of putamen; Gl = extirpation of oral pole of globus pallidus; Pr U = undercutting of 'premotor' cortex; Rt = right; Lt = left.

The patient with oculogyric crises and dystonia of the tongue and jaw was subjected to two operative procedures in which the medial portion of the left cerebral peduncle was severed in the endeavor to ameliorate her dystonic movements. The line of section envisioned by the operator and his assistants is illustrated in figure 3. Since this patient is still living, pathologic confirmation of the envisioned section is not available. Her neurologic status was evaluated pre- and postoperatively as was the case with the parkinsonian subjects.

RESULTS

As determined by clinical neurological examination, the data derived from this series of 15 hyperkinetic patients fail to demonstrate any neurologic deficit consequent upon surgical section of structures generally presumed to transmit the frontocorticopontine tract, namely, the anterior limb of the internal capsule and the medial two-fifths of the mesencephalic peduncle. Two representative cases are abstracted below.

Case 1.—J. S., aged 23 years, an unmarried girl of Polish extraction, was admitted to the hospital on January 4, 1942, complaining of coarse tremors, increasing stiffness and disability of the right-sided limbs. The symptoms had appeared first in the right hand approximately three years before and had always been more marked in this member than in the lower limb. Slowly progressive in character during the first two years, they had apparently come to a standstill during the eight months prior to the patient's hospitalization. Various belladonna derivatives, vitamin B_6 and barbiturates had proved ineffective. The patient appeared to be more concerned over the social and economic handicaps occasioned by her tremors than by the physical disability itself. The past personal and family histories were noncontributory.

*The remainder of the parkinsonian series[25] consisted of 15 patients subjected to pallidofugal section alone and one patient in whom a linear cortico-subcortical section between the 'motor' and 'premotor' cortex was carried out, followed by undercutting of the 'premotor' cortex and extirpation of the head of the caudate nucleus. Among those subjected to pallidofugal section three died following operation, bringing the total operative deaths for the entire series to six (15.7 per cent).

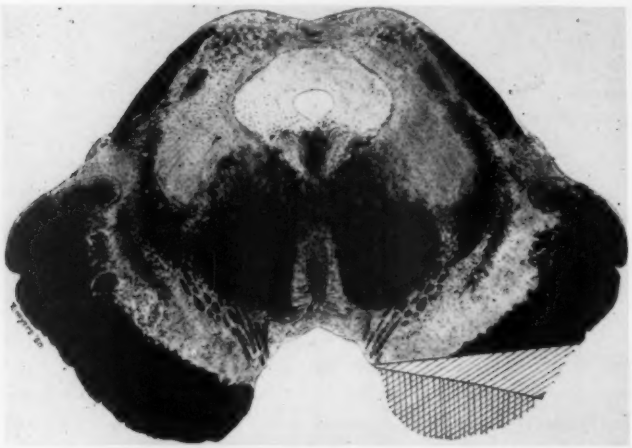


FIG. 3. Cross-section of midbrain at level of ventral tegmental decussation just posterior to emergence of oculomotor nerves to indicate the portion of left peduncle incised in patient L. W. Crossed lines indicate region sectioned at first operation, February 10, 1950; oblique lines indicate region sectioned at second operation, February 28, 1950.

Physical examination disclosed a well nourished, athletic type female in her early twenties, alert, intelligent and cooperative. The significant physical findings were confined to the nervous system.

A typical alternating tremor having a rate of 4½ oscillations per second and an excursion estimated at 5 to 8 degrees involved the right upper and lower extremities in repose. The tremor was variable from time to time in its conspicuousness. It was exaggerated under observation, emotion and efforts to overcome it and was suppressed during the execution of voluntary acts. It was completely absent during sleep.

The flail test revealed moderate hypertonicity of the upper and lower limbs. This observation was confirmed by the demonstration of slight but definite defects in the initiation, speed, extent of excursion and vigor of movements executed by the several members of the right upper limb as compared with their fellows. The safety pin test[25] for eupraxia was sluggishly but successfully executed by the right hand. Quick-succession movements on the right side were somewhat defective. When the patient walked, the right upper limb did not swing through as great an arc as exhibited by the left. The remainder of the neurological examination was completely negative.

Laboratory studies of the blood, urine and spinal fluid and roentgenograms of the skull and chest proved negative.

Operation, January 8, 1942. A small scalp flap was reflected within the hair line over the left frontovertical region. Corresponding bone and dural flaps were reflected and the left lateral ventricle was entered through a parasagittal incision 3 cm. in length and approximately 2 cm. from the falx.[23, 24] The ependyma overlying the superior margin of the head of the caudate nucleus was now incised and all available portions of the caudate head were extirpated by 'peeling' and the use of a fine suction tip. This exposed the medial aspect of the anterior limb of the internal capsule. By the use

of a slender nerve hook this structure was sectioned in curvilinear fashion as far posteriorly as the genu of the capsule (figure 1).

Subsequent Course. The patient's postoperative course was uneventful and she was discharged after several intensive neurologic examinations and cinematography had been carried out. These examinations together with several follow-up studies failed to disclose any neurologic disturbances ascribable to surgical section of the anterior capsular limb. The patient was free of tremors and the rigidity of the right-sided limbs, while still apparent, was noticeably improved. Motor power was essentially the same as noted preoperatively; the deep and superficial reflexes were unaltered; and all modalities of sensation, both crude and discriminatory, were preserved. All tests of equilibratory and nonequilibratory coordination were met satisfactorily. The patient could execute the safety pin test; catch, throw and repeatedly bounce a rubber ball; stand on one foot; hop; and perform a solo dance with apparently normal synergy and grace. The 'swing' of the right upper limb during walking was perceptibly improved but still slightly diminished as compared to that exhibited on the left.

Comment. The curvilinear incision through the exposed anterior capsular limb interrupted that segment usually presumed to transmit the frontocorticopontine fibers. No neurologic deficits properly ascribable to the procedure were demonstrable. The latter observation suggested, among other things, that the functions imputed by certain writers to the frontocorticopontine tract do not hold for the human; or that the frontocorticopontine fibers subserving such functions do not actually course through the anterior capsular limb as represented in many textbooks.

Case 2.—L. W., a housewife aged 39 years, was admitted to the hospital on February 7, 1950, complaining of almost continuous, involuntary contortions of the face and tongue. Though in themselves painless, these spasms had necessitated removal of all teeth to prevent trauma to the gums, lips, tongue and cheek. They frequently interfered with respiration and were in addition a source of much social embarrassment. The onset of the disorder occurred in March 1930 when the patient was 19 years old. Five years later, she experienced the first of a series of oculogyric crises in which the upturned eyes remained fixed for from one to several hours approximately twice a week. During sleep the patient was free of abnormal movements.

The only event of etiological importance in the past history was that following close upon an attack of scarlet fever during the winter of 1918-19 the patient suffered an attack of acute influenza.

She had been followed for many years as an in- and outpatient on the neurological service. Psychiatric clearance had been given on several occasions. No appreciable benefit had been obtained from hyoscine, hyoscyamus, stramonium, bromides, barbiturates, Benzedrine and Tolserol administered singly or in combination. Physiotherapy had proved equally ineffectual.

Physical examination disclosed a slender but well nourished, alert, intelligent and cooperative white woman appearing somewhat older than her stated age. She exhibited severe, non-patterned grimaces in which the lower jaw at times remained 'locked' open for 10 to 30 seconds. On other occasions the lower jaw jutted forward and clamped tightly against the upper. This circumstance, in the absence of teeth, imposed a

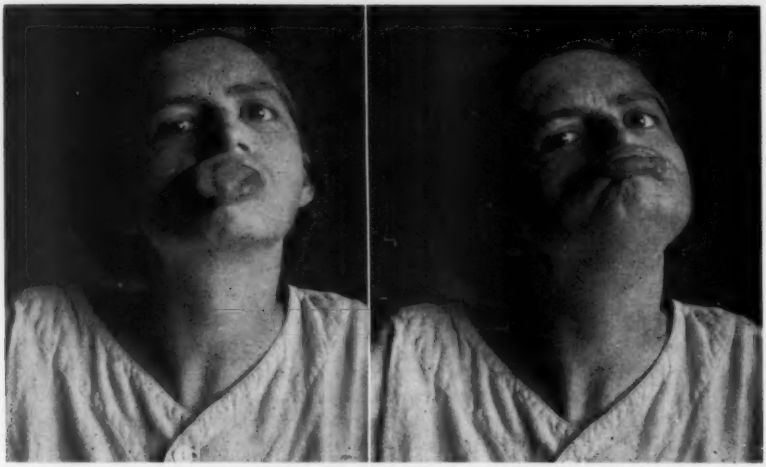


FIG. 4. Two of several dystonic patterns exhibited by patient L. W. *Left*, lower jaw open, tongue protruding to right; *Right*, lower jaw forcefully closed and protruded with tongue caught between gums, forcing lower lip across nares and interfering with respiration.

grotesque, passive posture upon the lips. The muscles of facial expression of the lower half of the face participated in the dystonic movements somewhat less frequently than the jaw. Periodically, the tongue emerged from the mouth, directly forward or to the right or left. At other times it was forcibly retracted. When, as frequently happened, the tongue pushed forward immediately before tonic closure of the jaws occurred, the upper lip was displaced upward, completely occluding the nares (figure 4) and impeding respiration to such an extent that the patient was under the necessity of elevating the ala nasi with her left index finger. Dorsiflexion of the neck was frequently in evidence, especially when the jaw protruded.

Except for occasional respites of a half minute or so, the described movements were constantly present, rendering speech severely dysarthric (at times completely unintelligible) and chewing and swallowing awkward. The 'voluntary' motor functions of the third, fourth, fifth, sixth, seventh, ninth, eleventh and twelfth cranial nerves as demonstrated during periods of respite were preserved.

In addition to the grimaces described above, a fine tremor was noted when the digits of the right hand were extended. The index finger tended to remain extended at all times and was poorly controlled. Nevertheless, writing could be performed with facility, the pen or pencil being held effectively between the thumb, middle and ring fingers. Owing to the severe dysarthria, much of the patient's emissive communication had to be accomplished by writing. Quick-succession tests and passive flailing of the limbs demonstrated a slight increase in muscle tone of the right hand and forearm.

Motor power appeared well preserved in corresponding members through the body, the limbs of the right side being slightly weaker than their fellows on the left.

The finger-to-nose, finger-to-finger, heel-to-shin, finger-pursuit and hopping tests revealed no clinical evidence of asynergy or dysmetria. The posture-holding and rebound

tests were well performed bilaterally. Equilibratory coordination, as determined by the Romberg, tandem-stance and oculokinetic tests, was likewise preserved.

The deep and superficial reflexes were present and equally active at corresponding regions throughout the body. The knee jerk was overly brisk bilaterally and an unsustained ankle clonus was demonstrable on the right side. Both plantar reflexes were flexor in type. No 'confirmatory' Babinski signs were elicitable.

Laboratory tests of the urine, blood and spinal fluid and roentgenograms of the head and chest were considered negative.

Study by clinical and slow-motion picture analyses of the dystonic movements warranted the inference that abnormal impulses were reaching the trigeminal, facial and hypoglossal motor nuclei via some upper motor neuron pathway. It was postulated that the medial corticobulbar tract might transmit these impulses and that, if so, its interruption might prove salutary. The decision to section the tract on the left side was reached in consideration of the only lateralizing data available, namely, the positive signs exhibited in the right hand and foot.

Operation, February 10, 1950. Accordingly, after apprising the patient and her family of the experimental character of the procedure, a low temporal flap was reflected on the left side under nitrous oxide-Pentothal anesthesia. The left temporal lobe was elevated, the bridging veins were clipped, coagulated and severed, and the incisura of the cerebellar tentorium identified. The arachnoid over the lateral aspect of the left peduncle was teased away to afford a clear view of the third and fourth nerves and the posterior cerebral and superior cerebellar vessels. By means of a curved blade, an incision 5 mm. deep was made into the medial portion of the left peduncle, immediately posterior to the emergence of the oculomotor nerve (figure 3).

Except for a transient paresis of the intrinsic and extrinsic oculomotor functions which lasted two days and a partial aphasia which lasted from the second to the seventh day, the patient's postoperative course was uneventful. She was free of all grimaces until the fourth postoperative day. During this period the tongue and lips could be moved satisfactorily to verbal direction. There was an exhaustible Babinski toe sign on the right, but no 'confirmatory' signs were elicitable. Nine days after operation the patient was able to crochet with her customary skill. Meanwhile, the dystonic movements had resumed their previous vigor and on the thirteenth postoperative day an oculogyric spasm lasting a half minute occurred.

Second Operation, February 28, 1950. Acting on the assumption that the first pedunculotomy might have been overconservative, the operator re-elevated the bone flap as before and deepened and lengthened the original incision, making it approximately 10 mm. deep and 15 mm. long (figure 3).

Recovery was uneventful. The dystonic movements reappeared on the second postoperative day. This time there was no dysphasia.

Complete neurologic examinations were carried out on March 5 and June 2, 1950. Without recording their details, it can be briefly stated that no new neurologic signs could be added to those described prior to the first operation. The patient was able to execute the safety pin test deftly with each hand unaided and could write with effectually the same facility as before operation (figure 5).

Comment: The cross sectional area of the pedunculotomy envisioned in this patient amply includes that segment in which the frontocortico-pontine fibers are said to be distributed. Following operation, no neuro-

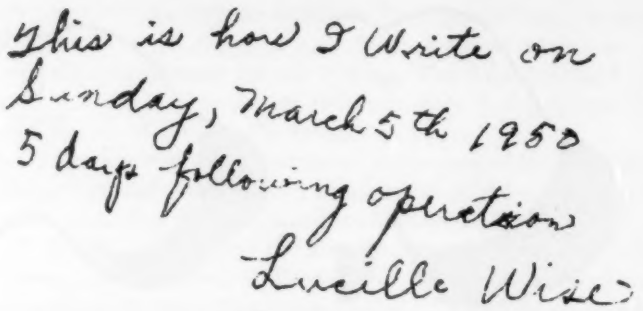


FIG. 5. Postoperative specimen of handwriting of patient L.W., illustrating no loss of eupraxia following section of mesial two-fifths of left peduncle. (The pre- and postoperative specimens were indistinguishable.)

logic deficits properly ascribable to the interruption of this structure were demonstrable. It is, of course, apparent that until the patient's midbrain becomes available for histologic study, the case cannot be regarded as crucial in any final sense. Pending such study, if any credence is to be lent to the case it must be conditioned upon the operator's ability to recognize anatomic landmarks and execute the envisioned pedunculotomy. The operator is in no position to claim infallibility in this regard.

DISCUSSION

In consideration of the data derived from the present series, it appears that interruption of the frontocorticopontine tract in the human is followed by no clinically detectable neurologic disabilities. Before fully endorsing such a conclusion, however, it is requisite to establish that the frontopontine tract was indeed severed. In the absence of a postmortem specimen from the patient with the dystonia of the face, jaw and tongue this point cannot be proved; however, it seems a reasonable inference. And provided the incision was made as envisioned at the operating table, it must have interrupted the frontopontine tract, irrespective of whether the fibers under inquiry travel in the medial tenth,[16] fifth,[8, 9, 13, 14, 20, 32] fourth[6, 34] or third[33] of the peduncle and irrespective of their anatomic relations to neighboring tracts (figure 6).

In the instance of the parkinsonian patients in whom the anterior limb of the internal capsule was severed and for which postmortem verification was obtained in three cases, the inference that the frontopontine tract was severed is supportable only if frontopontine fibers actually run through the anterior limb. Here a difficulty arises, for while many

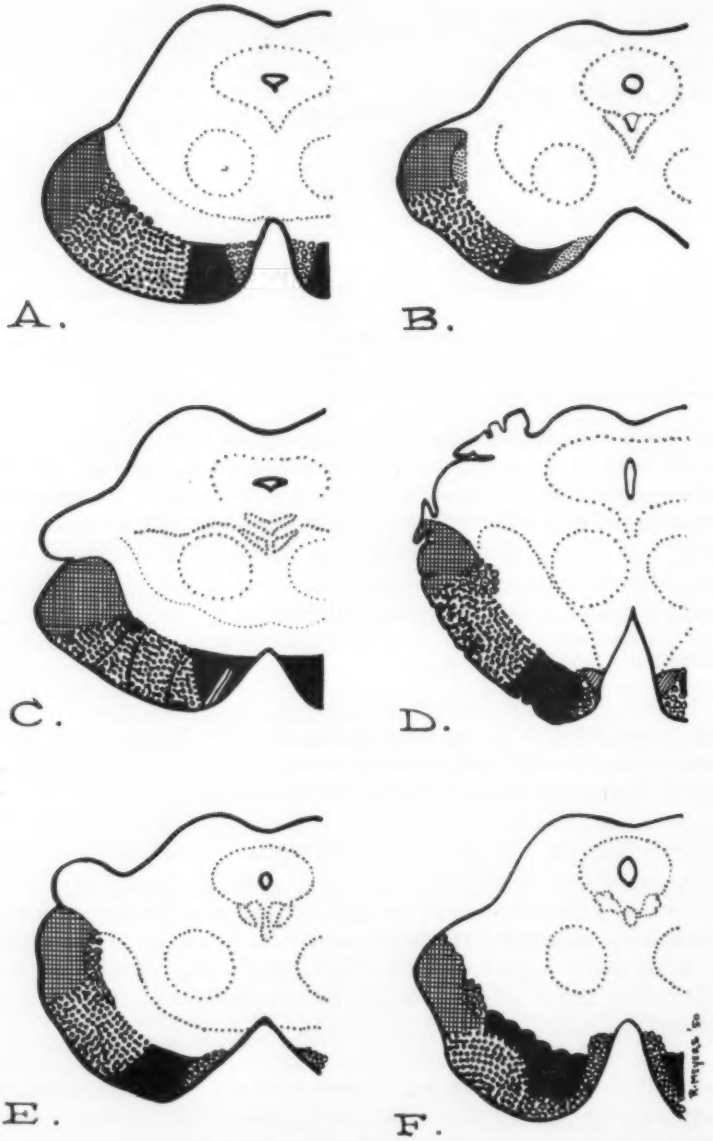


FIG. 6. *See legend opposite page.*

writers[6, 9, 13, 14, 20, 29] located the bundle in the anterior limb,* several[15, 16, 33, 34] describe it in the posterior limb. Such disparate claims are manifestly of prime significance for our inquiry. The data derived from the present series can be regarded as pertinent only if the human frontopontine fibers course through the anterior limb.

This difference of opinion concerning the course of the frontopontine tract in the internal capsule has a counterpart in the disparate current contentions regarding the cortical origin of the fibers. Some writers[2, 5, 13, 14, 19, 20, 21, 26, 29, 31, 35] consider that the fibers arise in the "prefrontal" cortex, overlapping and/or anterior to Brodmann's Area 8. Others contend that they arise mainly in Area 4;[39] Areas 4, 4-s and 6;[3, 8] Area 6;[6] or "just behind and just in front of the central sulcus."[11] Still others[9, 16] consider that frontopontine fibers originate from all three regions of the frontal lobe—"motor," "premotor" and "prefrontal."

It is likely that a part of the difficulty rests with terminology. Strictly speaking, the term "frontocorticopontine fibers" is applicable to any neuronic processes whose cell bodies are located in the cortex anterior to the rolandic fissure and whose terminal axons or collaterals play upon pontine nuclei. Taken literally, it includes elements derived from layer V of the "motor" cortex and distributed with the corticobulbar and corticospinal tracts. There is general agreement that the latter tracts course in the posterior limb of the internal capsule. In ordinary usage, however, these are not regarded as constituents of Arnold's bundle. Mettler's[20] suggestion, that fibers arising from Brodmann's Areas 4 and 6 and playing upon pontine nuclei be designated by the term "centropontine," promises to resolve some of the disputation. It cannot, however, resolve the issue for those who, like Sunderland,[33] insist that in the monkey all frontopontine fibers pass through the posterior limb.

If, for purposes of discussion, we assume Arnold's bundle to have been interrupted as surmised in the patients of the present series, it follows

*Among those who locate the frontocorticopontine pathway in the anterior limb there is some disagreement as to just where they run in relation to the thalamofrontal-frontothalamic bundle. Mettler[20] represents it anterior and Krieg,[13] posterior to that radiation.

FIG. 6. (left) Diagrams of midbrain, redrawn from six standard textbooks, to illustrate various positions and neighboring anatomic relationships in which the frontocorticopontine tract is represented. A, from Kuntz, fig. 176; B, from Strong and Elwyn, fig. 223; C, from Brodal, fig. 22; D, from Mettler, fig. 246; E, from Buchanan, fig. 89; F, from Herrick, fig. 80. Solid black = frontocorticopontine tract; cross-hatching = temporo-parieto-occipitocorticopontine tract; solid circlets = pyramidal tract; empty circlets = medial corticobulbar tract; circlets with dots = lateral corticobulbar tract; fine stippling (B only) = medial and lateral pes leminiscus; oblique shading (D only) = olfactopeduncular tract.

that the doctrines of earlier writers concerning the neurologic disturbances that supervene upon damage to the tract, however true for subhuman species, cannot hold for man. The negative results of the present experiments do not, of course, mean that the tract has no function in the human. Bailey's remarks (cited above) are especially pertinent in this connection. It seems more likely that the frontal components of an extensive corticocerebellar complex share the conduction of neural impulses indispensable to the integrity of some as yet unidentified "function"; and that only when such impulses, mediated over frontal parietal, temporal and occipital corticofugal fibers, are blocked in sufficient numbers do clinically demonstrable derangements appear.

In view of the numerous prefrontal lobotomy operations now being performed, early resolution of some of the issues relative to the human appears realizable.[22] Careful microscopic studies like those recently reported by Meyer, Beck and McLardy[21] hold considerable promise for the investigator.

SUMMARY

1. Twenty-three adult patients were subjected to operative procedures in which structures commonly considered to give transit to the frontocorticopontine tract were severed. Of these, 15 appeared suitable for final inclusion in the present study. Fourteen had been subjected, among other procedures, to surgical section of the anterior limb of the internal capsule for the relief of parkinsonian tremor. The fifteenth had undergone section of the medial third of the mesencephalic peduncle for the relief of dystonia of the face, jaw and tongue. Detailed pre- and postoperative clinical neurologic assays were carried out on all subjects.

2. No neurologic deficits attributable to surgical interruption of the structures mentioned above were demonstrated. Specifically, disorders of muscle tonus, of release, patterning and energizing of skilled acts, of synergy, and of reciprocal innervation, asserted by various writers to result from damage to the frontocorticopontine tract, did not supervene. For all practical purposes, the operative procedure appeared to be without functional consequence.

3. The negative conclusions arising from this study cannot be taken as final inasmuch as they rest ultimately upon two assumptions which, for the present, are incapable of proof—(a) that surgical interruptions of the anterior capsular limb and the medial segment of the mesencephalic peduncle were accomplished as envisioned; and (b) that the frontocorticopontine tract traverses the anterior limb of the internal capsule. In regard to the former assumption, the evidence cannot be considered

complete until at least some of the patients are subjected to postmortem study. In regard to the latter, neuroanatomists are not at present in complete agreement. There is, however, reasonable expectation that current differences of opinion will soon be resolved by intensive histologic examination of such prefrontal lobotomized patients as come to autopsy.

REFERENCES

1. Abbie, A. A.: The projection of the forebrain on the pons and cerebellum, Proc. Roy. Soc. Lond. B. 115:504, 1934.
2. Ariens Kappers, C. U.; Huber, G. C., and Crosby, E. C.: The Comparative Anatomy of the Nervous System of Vertebrates including Man, New York, The Macmillan Co., 1936, vol. 1, p. 811.
3. Bailey, P., in Bucy, P. C.: The Precentral Motor Cortex, ed. 2, Urbana, Ill., The University of Illinois Press, 1949, pp. 278-291.
4. Bernis, W. J., and Spiegel, E. A.: Die Zentren der statischen Innervation und ihre Be-einflussung durch Klein-und grosshirn, Arb. a. d. neurol. Inst. a. d. Wien. Univ. 27:197-224, 1925.
5. Bertrand, I., and Smith, F.: Sur un type special d'atrophie croisée du cervelet, Rev. neurol. 2:554, 1933.
6. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 2, Baltimore, Williams and Wilkins, 1939, pp. 1399, 1418, and 1499.
7. Brodal, A., and Jansen, J.: The pontocerebellar projection in the rabbit and cat: experimental investigations, J. Comp. Neurol. 84:31, 1946.
8. Brodal, Alf: Neurological Anatomy in Relation to Clinical Medicine, London, Oxford University Press, 1948, pp. 44, 82, 115-117, 423.
9. Buchanan, A. R.: Functional Neuroanatomy, Philadelphia, Lea & Febiger, 1948, pp. 77-9, 95 and 132-141.
10. Déjerine, J. J.: Anatomie des Centres Nerveaux, Paris, J. Rueff et Cie, 1901, vol. 2, pp. 73-100.
11. Dow, R.: Cerebellar action potentials in response to stimulation of the cerebral cortex in monkeys and cats, J. Neurophysiol. 5:121, 1942.
12. Herrick, C. J.: An Introduction to Neurology, ed. 2, Philadelphia, W. B. Saunders, 1918, pp. 176 and 184.
13. Krieg, W. J. S.: Functional Neuroanatomy, Philadelphia, Blakiston Co., 1942, pp. 178-79, 396-97, 529 and 536.
14. Kuntz, A.: A Text-book of Neuroanatomy, ed. 4, Philadelphia, Lea & Febiger, 1945, pp. 195-196, 200, 207, 262-267, and 371.
15. Levin, P. M.: The efferent fibers of the frontal lobe of the monkey (macaca mulatta), J. Camp. Neur. 63:369, 1936.
16. Levin, P. M., in Bucy, P. C.: The Precentral Motor Cortex, ed. 2, Urbana, Ill., University of Illinois Press, 1949, pp. 134-148.
17. Masuda, N.: Über das Brückengrau des Menschen (Griseumpontis) und dessen nähere Beziehungen zum Kleinhirn und Grosshirn, Arb. a. d. hirnanat. Inst. Zürich 9:1, 1941.
18. Mellus, E. L.: Motor paths in the brain and cord of the monkey, J. Nerv. & Ment. Dis. 26:197, 1899.
19. Mettler, F. A.: Corticofugal fiber connections of the cortex of macaca mulatta: The frontal region, J. Comp. Neurol. 61: 509, 1936.
20. Mettler, F. A.: Neuroanatomy, St. Louis, C. V. Mosby, 1942, pp. 135, 163, 254, 295, 300-301, and 366-380.
21. Meyer, A.; Beck, E., and McLardy, T.: Prefrontal leucotomy: A neuroanatomical report, Brain. 70:18, 1947.
22. Meyer, A., and McLardy, T.: Discussion: Leucotomy as an instrument of research, Proc. Roy. Soc. Med. 40:141, 1947.
23. Meyers, R.: The modification of alternating tremors, rigidity and festination by surgery of the basal ganglia, A. Research Nerv. & Ment. Dis., Proc. (1940) 21:602, 1941.
24. Meyers, R.: Surgical interruption of the pallidofugal fibers: Its effect on the syndrome of paralysis agitans and technical considerations in its application, New York State J. Med. 42:317, 1942.
25. Meyers, R.: Surgical experiments in the therapy of certain "extrapyramidal" diseases: A current evaluation, Act psychiat. et neurol., Suppl. 67, 1, 1951.
26. Monakow, C. von: Gehirnpathologie, In Nothnagel's Spezielle Pathologie u. Therapie, Vienna, A. Holder, 1905, vol. 9, pt. 1.

27. Papez, J. W.; Bennett, A. E., and Cash, P. T.: Hemichorea (hemiballismus): Association with a pallidal lesion, involving afferent and efferent connections of the subthalamic nucleus; curare therapy, Arch. Neur. & Psychiat. 47:667, 1942.
28. Pfeiffer, R. A.: Myelogenetisch—anatomische Untersuchungen über den Zentralen Abschnitt der Taststrahlung, der Pyramidenbahn, der Hirnnerven und Zusätslicher Motorischer Bahnen, Nova Acta Leopoldina N. F. 1:341, 1934. (Cited by Bailey.)
29. Rutishaüser, F.: Experimenteller Beitrag zur Stabkranzfaserung in Frontalhirn des Affen, Monatschr. f. Psychiat. u. Neurol. 5:161, 1899.
30. Simpson, S.: Secondary degeneration following unilateral lesions of the cortex, Intern. Monatschr. f. Anat. u. Physiol. 19: 304, 1902.
31. Smith, G. E.: The Evolution of Man, ed. 2, London, Oxford University Press. 1927, pp. 161-164.
32. Strong, O., and Elwyn, A.: Human Neuroanatomy, ed. 2, Baltimore, Williams and Wilkins, 1948, pp. 210, 246, 251, 257, 259, and 284-285.
33. Sunderland, S.: The projection of the cerebral cortex on the pons and cerebellum in the macaque monkey, J. Anat. 74:201, 1940.
34. Verhaart, W. J. C., and Kennard, M. A.: Corticofugal degeneration following thermocoagulation of areas 4, 6 and 4-S in macaca mulatta, J. Anat. 74:239, 1940.
35. Von Bonin, G.: Essay on the Cerebral Cortex, Springfield, Ill., Charles C Thomas, 1950, pp. 72, 101-104, and 112.
36. Warner, W. P., and Olmsted, J. M. D.: Influence of cerebrum and cerebellum on extensor rigidity, Brain. 46:189, 1923.
37. Weed, L.: Observations upon decerebrate rigidity, J. Physiol. 48:205, 1914.
38. Wilson, S. A. K.: On decerebrate rigidity in man and the occurrence of tonic fits, Brain. 40:220, 1920.
39. Winkelman, N. W., and Eckel, J. L.: Origin of the cortico-cerebellar system as determined in human pathological material, A. Research Nerv. & Ment. Dis., Proc. 6:481, 1926.

The brain is divided into two portions, a superior and inferior, or the greater and lesser brain. The greater is called the cerebrum, the lesser the cerebellum. These are separated, to a considerable extent, by a thick strong membrane, stretched horizontally across from one side of the skull to the other, and which is but a fold of the dura mater, or of that membrane that lines the interior of the skull. The membrane which thus separates the greater from the lesser brain is called the tentorium and serves to protect the lesser brain, the medulla oblongata and the upper or greater brain. Both the cerebrum and the cerebellum are divided into halves or hemispheres to a considerable extent. They are thus separated by a perpendicular fold of the dura mater called the falx, and which may serve to protect one side of the brain from the weight or concussion of the other.

—Amariah Brigham in *An Inquiry concerning the Diseases and Functions of the Brain, the Spinal Cord and the Nerves*, published in 1840.

Phenomena and Correlates of the Psychomotor Triad

William G. Lennox, M.D.

THE psychomotor epilepsies are a crossroads, a meeting ground, for various disciplines and research-minded men. This relatively unexplored subject engages the interest of the anatomist, the brain surgeon, the neurophysiologist, the psychiatrist and the family physician who must treat the baffling symptoms. Anatomical significance has been contributed through the work of many men, but principally those intrepid pioneers—Penfield and the Gibbs. They have tracked some of the seizure phenomena of which we shall speak to their anatomical origin, Penfield by patient mapping of stimulation points of the temporal lobe and its environs, the Gibbs by applying electrodes over this area with sleeping patients.

A survey of new data calls for orientation and perspective. We must not only classify clinical symptoms, but we must correlate these with the deep workings of the brain and mind, since widely diverse symptoms and appearances may rest on a common ground of origin or of mechanisms. Witness, for example, three seizure patterns that are most unlike—namely, a brief blackout of consciousness, a quick jerk of an extremity or a sudden collapse of posture. Yet, these three, connected by a common bond of dart-dome wave pattern and response to Tridione therapy, belong together in a petit mal triad.[1]

CORRELATING CONDITIONS

The sphere of knowledge for epilepsy may be represented as a circle comprised of seven different areas of interest.[2] In figure 1, the lighter

From the department of neurology, Harvard Medical School and the Children's Medical Center, Boston.

Read before a joint symposium of the American Academy of Neurology and the American League Against Epilepsy, Cincinnati, Ohio, April 15, 1950.

This is No. LVIII in "Studies in Epilepsy." It was aided by research grants from the National Institute of Mental Health of the National Institutes of Health, U.S. Public Health Service, and from the Rockefeller Foundation.

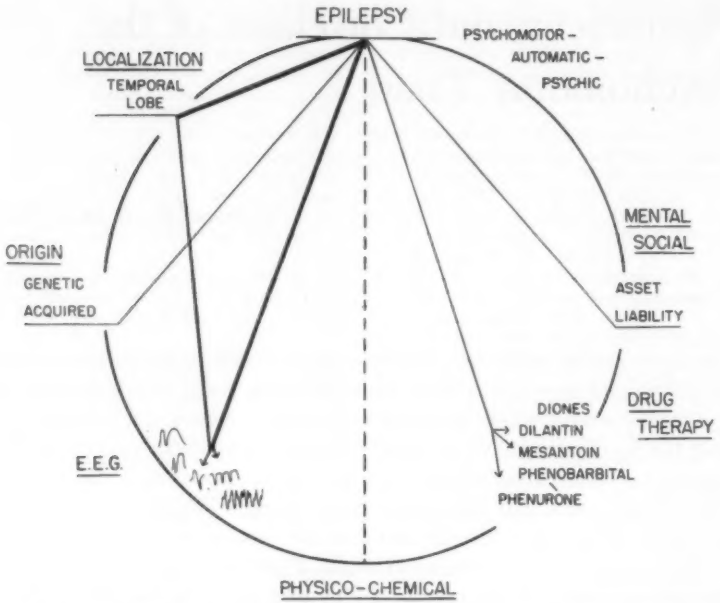


FIG. 1. Seven areas of interrelated interest in epilepsy represented as points on the circumference of a circle. At the top, there are clinically observed seizures, and proceeding clockwise, mental or social status, drug therapy, physico-chemical substrates, EEG findings, the origin and the cerebral localizations of the components of a seizure. The heavy triangle joins the areas of principal interest in the psychomotor epilepsies: the descriptive manifestations, the spike or high voltage slow discharges of the EEG, and the temporal lobe.

lines of the chart go to areas only partially explored. Thus, at three o'clock on the chart, persons subject to psychomotor seizures, more than those with other types, are prone to be liabilities, socially and mentally. At five o'clock, response to medication is relatively non-specific; at six o'clock little, if anything, is known about the physico-chemical background of this form of seizure; at nine o'clock, acquired causes of seizures are more prominent than genetic causes. However, main interest is centered in the heavy triangle that unites the descriptive, the anatomical and the electroencephalographic findings.

DISTRIBUTION OF SEIZURE PATTERNS

Let us consider next the proportionate representation of psychomotor seizures in epilepsy. The distribution of seizure types and combinations of types among 1900 office patients is shown in figure 2. The distribution is

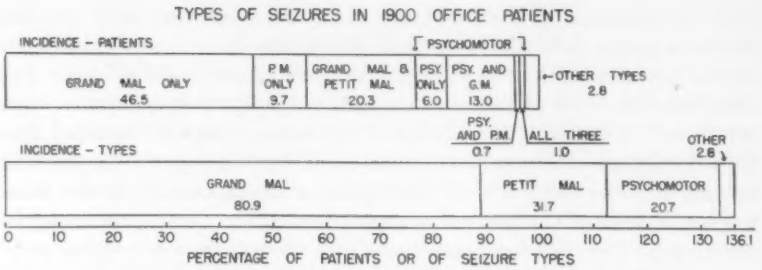

TYPES OF SEIZURES IN 1900 OFFICE PATIENTS
INCIDENCE – PATIENTS
PSYCHOMOTOR
GRAND MAL ONLY 46.5
P.M. ONLY 9.7
GRAND MAL & PETIT MAL 20.3
PSY. ONLY 6.0
PSY. AND G.M. 13.0
OTHER TYPES 2.8
PSY. AND P.M. 0.7
ALL THREE 1.0
OTHER 2.8
INCIDENCE – TYPES
GRAND MAL 80.9
PETIT MAL 31.7
PSYCHOMOTOR 20.7
0 10 20 30 40 50 60 70 80 90 100 110 120 130 136.1
PERCENTAGE OF PATIENTS OR OF SEIZURE TYPES

FIG. 2. Distribution of types of seizures or of combinations of types in 1900 patients (upper bar), and the distribution of 518 seizure patterns in these patients (lower bar).

as follows: psychomotor alone, 6.0 per cent; psychomotor and grand mal, 13.0 per cent; psychomotor and petit mal, 0.7 per cent; all three types, 1.0 per cent. Thus, 20.7 per cent of patients had a history of psychomotor attacks, with or without some other seizure pattern. Grand mal alone occurred in 46.5 per cent; grand mal and petit mal in 20.3 per cent; petit mal alone in 9.7 per cent; and some other type, usually autonomic, in 2.8 per cent. Striking is the tendency of convulsions and psychomotor seizures to occur in combination (63 per cent of patients with psychomotor) and the lack of such agglutination on the part of petit mal and psychomotor (3 per cent). A reason for this discrimination will be discussed later. Considering types of seizures, the distribution was as follows: grand mal, 80.9 per cent; petit mal, 31.7 per cent; psychomotor, 20.7 per cent; other types, 2.8 per cent—a total of 136.1 per cent. The excess over 100 per cent represents patients with a history of more than one type of seizure.

DESCRIPTIVE PHENOMENA

Historical. The remarkably modernistic treatise of Hippocrates, "The Sacred Disease," describes what sounds like automatisms, nocturnal psychomotor seizures and epilepsia procursiva: "And I see men become mad and demented from no manifest cause, and at the same time doing many things out of place; and I have known many persons in sleep groaning and crying out, some in a state of suffocation, some jumping up and fleeing out of doors, and deprived of their reason till they awaken, and afterwards becoming well and rational as before, although they be pale and weak; and this will happen not once but frequently."

In later centuries when the "falling sickness" predicated a fall which initiated a convulsion, psychomotor attacks are rarely identifiable. Aretaeus,[3] an authority of the second century, plainly described hallucinations of sight, hearing and smell as a precursor of a seizure: "But if it be

near the accession of the paroxysm there are before the sight circular flashes of purple or black colors or all mixed together so as to exhibit the appearance of a rainbow expanded in the heaven; noises in the ears; but sometimes the smell of heavy odors such as the agate stone makes them fall down." Presumably knowledge of this aura prompted the belief that the convulsions of a purchased slave could be "activated" by smell of burning jet. The first recorded description of automatism is in the Rosa Anglica of John of Gaddesden[4] written about 1314: "And sometimes the paroxysm is short as I have sometimes seen when there was nothing to be done save that the patient would set his back to the wall or sit down and hold his forehead with his hand and rub his face . . . then the patient himself stood up and recited the Lord's Prayer and spat once and threw off the paroxysm. And frequently during the day sometimes it came as I saw in one monk frequently at dinner or supper, and he did not cure it nor did outsiders perceive it save rarely." Prichard in 1822 described ambulatory automatisms: "A most unusual circumstance in the history of epilepsy is the appearance of a species of somnambulism or of a kind of ecstasis during which the patient is in an undisturbed reverie and walks about fancying himself occupied in some of his customary amusements or avocations. This takes place during the waking as well as the sleep hours—where they do not coexist with epilepsy, they often seem to stand in the place of it and to depend on those particular circumstances of the constitution which are the fundamental causes of epilepsy." Most physicians have required that, to be classified as epileptics, patients having automatisms must give a history of grand mal also. However, Richard Bright[5] in 1831 diagnosed a man as epileptic, although grand mal had never been observed. The patient "became delirious and wandered in the street without hat or coat, walking in a state of complete unconsciousness from Clapham common to Chorediteh and was between four and five hours on the road" when intelligence returned.

Nomenclature. Various names have been applied to manifestations of epilepsy which are not convulsive and not petit mal. Only in the last century or two has it been suggested that a period of mania or maniacal behavior might be considered an epileptic seizure. According to Mead,[6] Tyson (1650-1708), a physician at the Bethlehem Hospital, called patients subject to attacks of fury "epileptick mad." Falret called periods of mania "grand mal intellectual." Prichard stated that in some instances "epileptic delirium" could appear without any previous fit. P. Janet used "psycholepsy" to designate altered consciousness or dream states. In 1862, according to Turner,[7] Hoffmann used the term "psychical equivalent." However, these words did not gain acceptance until after 1900. Gower's fine

book, published in that year, does not use them. Wilson[8] proposed "psychic variant" because, he argued, this form of seizure is not an equivalent of epilepsy, but is epilepsy. However, the Gibbs and Lennox,[9] describing the electroencephalographic findings in such cases in 1938, felt that the term psychic did not take account of the motor activities that many patients displayed and adopted the word "psychomotor." At some future time, "temporal epilepsy" might supplant the present confused terminology.

THE PSYCHOMOTOR TRIAD (temporal epilepsy)

The term "psychomotor" has been accepted with reservation by many students of epilepsy. Indeed, the clinical phenomena are too diverse to be encompassed in a single word. No one word seems broad enough to describe the various phenomena encountered. In any grouping, overlapping of symptom complexes will appear. A given patient may present a variety of symptoms. The attempt at classification that follows is for the purpose of discussion and possible clarification. Three main subdivisions are suggested, each labeled on the basis of the predominance of motor or of psychic manifestations. We then have a psychomotor (or temporal lobe) triad corresponding to a convulsive and a petit mal triad. The first of these subdivisions we may call "psychomotor," the second, "automatic" and the third, "psychic" or "subjective." In addition, two or three subgroups are needed for each.

A. *Psychomotor.* Seizures display either excess or absence of involuntary motor activity in combination with amnesia for the events that transpire.

1. Increased tonicity or a rigidity of muscles (without clonus), but oftentimes with an adversive movement of the head or eyes or with torsion spasm or primitive automatisms such as chewing, swallowing, sucking, smacking or licking the lips, mumbling or drooling, acts called masticatory. Mild cyanosis often accompanies this type of seizure. Posture is usually maintained. Unconsciousness and amnesia are usually complete. The symptom complex may be confused with a mild convulsion (grand mal).

2. Excessive muscular or psychic activity with manic or psychotic episodes, fugues, running fits, paroxysmal bad behavior and nightmares—the contact of the person with his environment and memory for the events is impaired. These states must be differentiated from hysteria, emotional outbursts, manic psychosis, criminality, psychotic personality, compulsive drinking or simply a "bad boy."

This subgroup is the least clearly defined and the most controversial of all. Many of the manifestations are automatisms in which motor phenomena are excessive. In others an abnormal state of the mind overshadows abnormal physical activity. Psychotic or bad behavior may precede or succeed a convulsion or may recur paroxysmally without attending seizure of another sort. In this last event many persons question whether the abnormal display should be termed epileptic. Maudsley[10] in 1874 made this clear statement, "Instead of the morbid action affecting the nervous centers and issuing in a paroxysm of convulsions, it fixes on the mind centers and issues in a paroxysm of mania which is so-to-speak an epilepsy of the mind."

Today doubtful cases may be brought before the judgment seat of the electroencephalogram to determine the presence or absence of temporal lobe spiking or other abnormalities of brain function. Also Penfield[11] reproduced the spontaneous seizures of a patient with previous brain injury by electrical stimulation on the triangular gyrus of a frontal lobe. Attacks consisted of confusion, weeping, violent struggling that required three men to control, with amnesia for the event.

"Behavior problem" children are a concern to parents and neighbors, but more important to the general public are criminal acts that might be epileptic. Legal personnel and procedures are widely involved. Criteria denoting irresponsibility have been concisely expressed by Maudsley;[10] "a murder committed suddenly without premeditation, malice or motive, openly, and in a way quite different from the way in which murders are commonly done." Amnesia, or blurred memory for the event, should, of course, be added. Illustrative cases and references appear in a previous paper.[12] The electroencephalographic findings in prisoners charged with murder have been reported by Stafford-Clark and Taylor.[13]

3. Arrest of motion (without muscular tonus), periods of immobility or slumping, with staring, stupor, trance or sleep-like states. Masticatory acts may attend. Consciousness is impaired or absent. Seizures are distinguished from petit mal because of the lack of abrupt beginning and ending and the absence of clonic movements. They may not be distinguished from phenomena that accompany a slow spike-wave discharge except by the electroencephalogram.[14]

B. *Automatic.* Automatisms, with amnesia for the events. Two subgroups are distinguished on the basis of the person's apparent awareness and the extent of his contact with his environment.

1. Awareness and self command is clearly impaired. The seizure consists of automatisms, ambulatory or else repetitious manipulations, such as unbuttoning the clothes, or opening and shutting a purse. The speech is

blurred or irrelevant; the person appears confused or intoxicated; his actions are inept, purposeless or inappropriate, usually a diversion from what he has been doing. Precision and thoughtfulness of speech or actions are lacking. The following may require differentiation: intoxication, hypoglycemia, sleep walking, psychosis and petit mal status. The last named is illustrated by the following case.

A 12 year old boy had frequent and prolonged periods of confusion which usually came on when he was being transported by streetcar or automobile. Attacks could be precipitated in this way. Although he could be led about, he could not speak or obey simple commands and was amnesic for the period of confusion. His routine electroencephalogram was not distinctive. For several years these confused periods were classified as psychic seizures. Then a recording was secured during a period of confusion that lasted four hours. The brain waves from the frontal areas were almost continuously of the high voltage spike-wave pattern. This pattern and the confusion cleared after injection of Tridione. Therefore, the boy was having not a period of automatism, but a status of petite absence.

2. The person seems normal in appearance and activity. There is apparent full contact with environment and full retention of consciousness, and yet memory for the events of the period is gone. Such an attack may be confused with simple inattention, absent mindedness or excitement. To be differentiated also are: hysterical amnesia, fabrication, retrograde amnesia that blots out memory for events that preceded a convulsion, and amnesia associated with concussion or fever. The automatisms encountered in these two subgroups and the various degree of associated awareness are most intriguing. Many interesting and puzzling examples might be related. The book by Spratling[15] details cases of what he calls "psychic epilepsy."

A man who had a history of both severe grand mal and minor attacks was engaged in tying pamphlets into bundles. He desisted and walked hastily into the next room. His face was white, his expression was tense, his pupils dilated and insensitive to the light. The corneal reflex was blunted as was sensation all over the body. He seemed to be gazing into space without seeing anything. He entered a closet, picked up some pamphlets, counted and arranged them. Shown a watch and asked the time, he replied correctly. In walking about the room, he endeavored to pull a telephone wire from the floor and when told not to said, "Oh it must come up." Except for this incident, he was calm, obedient and orderly and the uninitiated observer would not have known he was having a seizure. He regained consciousness in 15 minutes without memory of his acts, but a headache indicated to him that an attack had occurred.

A commercial traveller had amnesia for a period of 28 days. During this time he travelled extensively, visited customers, wrote orders and telegrams as proved by copies of letters and daily entries in his diary. His behavior seemed normal, except that on certain days he kept to his room without obvious reason. Near the end of the period he had two or three grand mal seizures. The length of the period would argue against a retrograde amnesia.

A patient of Turner's[7] had paroxysmal headaches. He had a brother who had

experienced one convulsion. This patient lost all knowledge of his surroundings for a period of 10 days. During part of this time he carried on his ordinary duties. Members of the family noted only that he seemed quieter than usual and had a dazed appearance. He then disappeared and came to at a place 150 miles from London.

A war veteran subject to many automatisms read in the newspaper about a man who had embraced a strange woman in a park, followed her into a women's toilet and then boarded a bus. From the description given, he realized that he was the man. Another veteran came to in a distant city after an unremembered interval of weeks with an extra $500 in his possession. Other personally observed cases have been reported elsewhere.[16]

One of the most detailed and interesting accounts in the literature was written in 1888 by a physician about himself, a patient of John Hughlings Jackson.[17] In addition to a rare grand mal and frequent brief psychomotor attacks (A-1) and dream states, he performed at times complicated acts which should require awareness of surroundings and intact thought processes. Thus, a short period of amnesia that occurred while playing tennis did not alter the accuracy of his shots. Once an attack came on when he was skiing across a Swiss glacier. His mind was concentrated on his sensations rather than on his course, and when he regained his normal senses after a few minutes he looked back with surprise at the long slope of broken ice he had traversed, a course that normally would have been difficult for him. During another period of amnesia he completed a railway journey, walked half a mile to his home and came to searching his pocket for the key. Finally he experienced the aura of an attack while preparing to examine a child. He then found himself seated at a desk talking with another person. The child was later found in bed with a note "pneumonia of the left base" which the doctor had written, a diagnosis confirmed by a second examination.

A doctor patient aged 61 had a brother with epilepsy. One morning the doctor left home in answer to an emergency call from the hospital and returned several hours later a trifle confused, feeling as though he had experienced a bad dream. At the hospital he had performed a difficult podalic version and perineal repair with his usual competence, but later had done and said things deemed inappropriate. This episode was unmatched by any other in his past or later history.

C. *Subjective (psychic) seizures.* In contrast with the two previous groups, memory for the seizures of this group is retained. Symptoms are told by the patient and not by the onlooker, being subjective rather than objective. The attacks must be distinguished from neurosis, hysteria, psychosis or plain imagination.

1. Dream states, feelings of unreality or illusions. There may be *déjà vu* phenomena (the feeling that an event is being relived or a scene reviewed). Included also are brief periods of compulsive thinking or of laughing. The writings of Jackson[17] and Penfield[11] contain many illustrative cases and discussions of the neurophysiology involved. *Déjà vu* phenomena constituted the seizures or the aura of psychomotor or automatic seizures of Jackson's physician patient. The first of these was "a vivid and unexpected recollection—of what, I don't know." He records that in the abnormal state the recollection is more instantaneous, absorbing, vivid and satisfactory than normal memory; yet he is dimly

aware that the recollection is fictitious and afterwards cannot remember what he recalled.

2. Hallucinations. These are sensory, of sight, hearing, smell or taste. Visual hallucinatory aura such as Aretaeus[3] described may not be distinguishable from the hallucinations of opthalmic migraine; or objects may appear large or small, or unusually distinct. There may be tinnitus, or sounds may become louder or higher pitched. A peculiar smell or taste is usually unpleasant or cannot be described.

3. Mild confusion or disorientation, a feeling of strangeness without loss of consciousness or memory, and without motor component or masticatory acts, a "brown out," in contrast to a "black out." The person is cognizant of what is said or done, but cannot participate; he may be asphasic or unable to speak. Episodes are transitory and, like dream states and hallucinations, are subjective.

We should not speak of placing these diverse phenomena in pigeonholes or compartments. These eight divisions are like parcels of marshy ground that have been only recently surveyed. There are tentative mark-

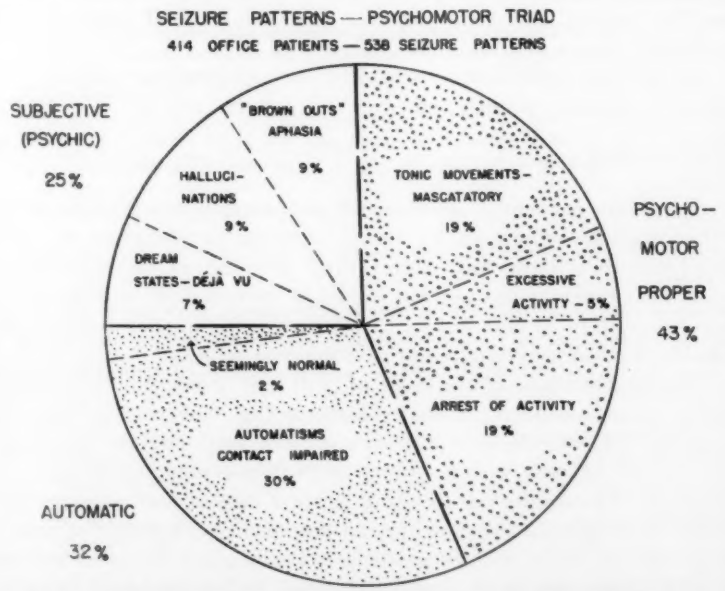


FIG. 3. Distribution of 538 psychomotor manifestations among eight classifications of seizure patterns. These appeared in 414 patients with a history of psychomotor epilepsy. The heavily dotted area denotes seizures classified as psychomotor, the lightly dotted area the automatic, and the clear area the subjective (psychic) seizures. Clinical divisions are explained in the text.

ers for boundary lines, but no dividing walls. The different seizure patterns vary in composition from time to time and from patient to patient. The distribution of the various phenomena will differ with respect to the character of the epileptic group, whether old or young, or whether attending a medical or a surgical clinic.

DISTRIBUTION OF THE PSYCHOMOTOR TRIAD

Figure 3 represents the distribution of these eight types of seizures in a group of 414 office patients who gave a history of having had 538 of the eight seizure patterns. An individual may have more than one pattern—for example, an automatism and a hallucination.

The three members of the psychomotor triad were represented as follows: psychomotor attacks, 43 per cent; automatic, 32 per cent, and subjective (psychic) seizures, 25 per cent. Because psychomotor seizures are represented most often, the name psychomotor epilepsies may, with reason, be applied to the total group. However, more specific assignment of seizure phenomena into psychomotor, automatic and subjective or psychic classifications seems desirable. Of the individual subgroups, evident automatisms was the largest, 30 per cent.

Of the various clinical correlates of the psychomotor epilepsies, two will be mentioned—namely, other seizure patterns and age.

SEIZURE CORRELATES

Sixty-three per cent of persons with some form of psychomotor epilepsy had experienced convulsions also. In contrast to this, there was additional history of petit mal in only three per cent of the psychomotor cases. That psychomotor seizures should be preceded or accompanied 20 times more often by convulsions than by petit mal implies a causal relationship between convulsive and psychomotor attacks.

The time relations of the onset of petit mal or psychomotor seizures and of grand mal gives further evidence of this. The year of onset was noted for 260 patients with a history of both petit mal and grand mal and for 250 patients with a history of both psychomotor seizures and grand mal. The results are shown in figure 4. Grand mal preceded petit mal in 25 per cent of the patients and preceded psychomotor seizures in 46 per cent, a nearly doubled incidence. (Leaving out the cases with onset in the same year, these percentages are 37 and 64 per cent.) As shown in the chart the interval between onset of grand mal and the later onset of the other type was much greater for psychomotor than for petit mal seizures. Thus, the proportion of petit mal or psychomotor seizures com-

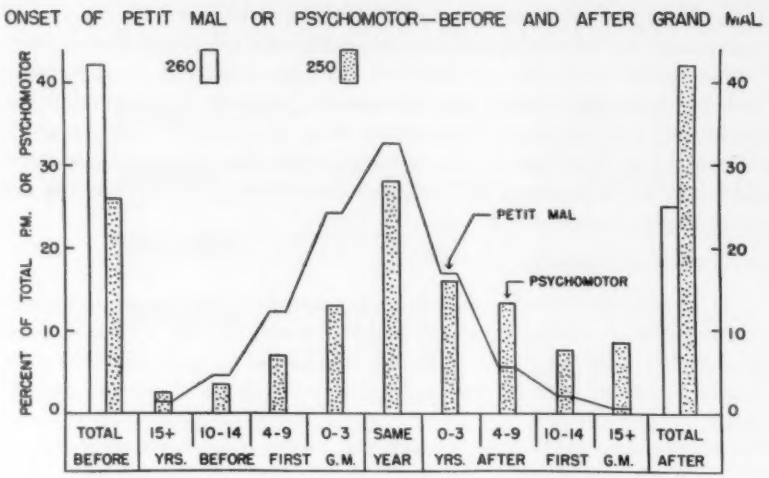


FIG. 4. Time relations in the onset of petit mal and psychomotor seizures with reference to the onset of convulsions. The blank columns refer to petit mal, the dotted columns to psychomotor seizures. The abscissa refers to years before or after the onset of grand mal. The ordinate measures the percentage of the 260 petit mal cases, or of the 250 psychomotor patients. The cases having the two types of seizures were picked at random from the files.

ing 10 or more years after the onset of convulsions was 2.7 per cent for the petit mal and 15.6 per cent for the psychomotor group.

INFLUENCE OF ANTECEDENT BRAIN PATHOLOGY

That organic changes play a part in the occurrence of psychomotor seizures and grand mal (in contrast with petit mal) is indicated by the proportion of patients having such forms of epilepsy who gave evidence of brain damage that antedated their epilepsy. The percentage of "organic" cases among 1,504 office patients was as follows:

TABLE 1

History of Seizure Types	*No. Patients*	*Per Cent "Organic"*
Psychomotor and grand mal	216	33.3
Grand mal alone	736	25.5
Grand mal and petit mal	285	20.3
Psychomotor alone	117	19.7
Petit mal alone	150	14.7

Antecedent brain injury was more than twice as common in patients with combined psychomotor and grand mal seizures as in patients having only petit mal. The cases were not analyzed in sufficient detail to determine the relative roles of the antecedent injury and the convulsions

in producing temporal epilepsy. Often there was history of one or a few convulsions in early childhood, possibly with some infectious disease, then nothing until one of the psychomotor epilepsies appeared in adolescence or beyond. In other cases, the psychomotor seizures would overlap the grand mal and then gradually replace them. Possibly the early convulsions and the attendant anoxia or blood vessel damage caused localized pathology in the region of the temporal lobe which, in time, produces the curious symptoms of the psychomotor triad.

INFLUENCE OF A GENETIC HISTORY

If, as suggested by the preceding data, acquired lesions are important in psychomotor epilepsy, a relatively sparse family history of epilepsy is to be expected. Following is the incidence of epilepsy among the 6,670 near relatives of 1,504 patients with reference to the types of seizures experienced.

TABLE 2

History of Seizure Types	*No. Relatives*	*Per Cent Epileptic*
Psychomotor alone	578	2.6
Psychomotor and grand mal	1,053	2.8
Grand mal alone	3,360	3.0
Petit mal alone	533	3.4
Grand mal and petit mal	1,137	5.4

Thus, patients with a history of having both grand mal and petit mal, had twice as many epileptic relatives as patients with a history of psychomotor seizures, either alone or combined with grand mal.

DISTRIBUTION OF TYPES OF SEIZURES AND AGE OF PATIENTS

Histories of the 1,900 office patients were studied to ascertain the relationship of a history of psychomotor attacks and the age of the patient when questioned (figure 5). As patients increase in age there is progressive increase in the proportion with a history of psychomotor seizures; 9.7 per cent in patients less than five years of age and 34.1 per cent in those above the age of 40. Furthermore, the greatest increase took place in patients who had had convulsions also—usually before the advent of psychomotor trouble. Convulsions had been present in 3.9 per cent of those less than 10 years and in 26.5 per cent of those over 40 years of age. The incidence of complicating petit mal did not increase with age. As shown in another report[18] which considers seizures of all types, psychomotor seizures and petit mal have a reciprocal relationship, the former increasing and the latter decreasing with increasing age. On the other hand, the incidence of psychomotor phenomena is about the same in males and females.

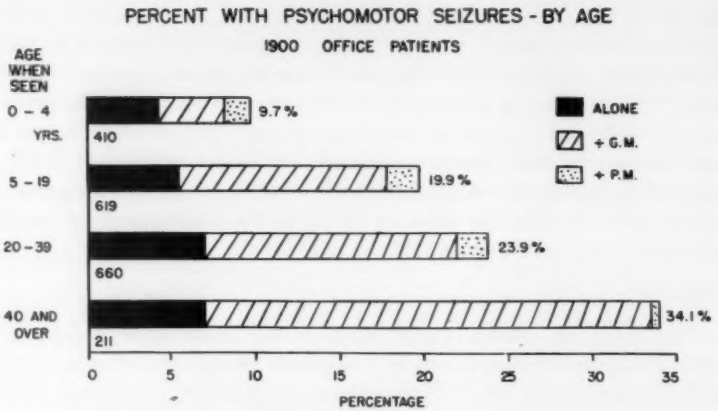


FIG. 5. (above) The proportion of 1900 office patients with a history of psychomotor seizures with reference to the patient's age at his first visit. The bars refer to various age groups. The solid portion represents those with psychomotor epilepsy only, the barred portion those with convulsions also, and the dotted portion those with petit mal also. The figures at the base of the bars indicate the number of all patients of that age, and the figures at the end of the bars represent the total percentage with a history of psychomotor epilepsy. Percentages for the four age groups are as follows: psychomotor alone, 4, 5, 7 and 7 per cent; combined with grand mal 4, 12, 15 and 26 per cent; combined with petit mal 1, 2, 2 and 5 per cent.

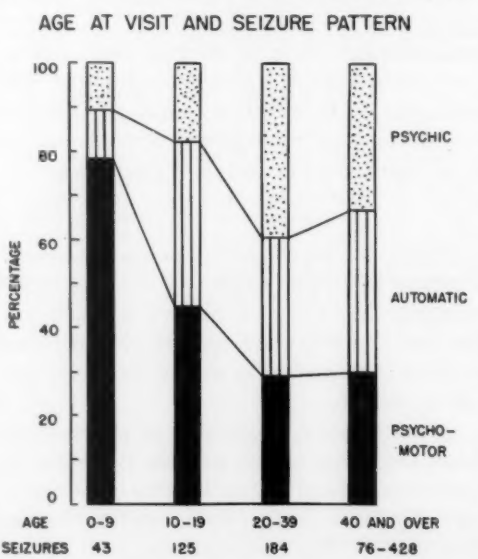


FIG. 6. (left) The distribution of the three subgroups of psychomotor seizures with reference to the age of patients at the first visit. The total number of patients was 414 and the seizure patterns, 544. The number in each age group is shown by the figure at base of each bar. Among those below ten years of age, seizure patterns were distributed as follows: psychomotor proper 78 per cent, automatic and subjective (psychic) each 11 per cent.

Is age influential in determining the subgroups of the psychomotor triad? In the present study, members of the psychomotor triad were distributed into three groups, based on the age of the patient at the time he was first seen. As shown in figure 6 the A group, comprising those attacks

that involve increase or arrest of movement (black portion of the columns), became progressively less frequent in the older age groups, while automatisms and subjective (psychic) manifestations became more frequent. Thus, in the age groups below 10 years and above 40, the percentage of psychomotor patterns was, respectively, 78 per cent and 30 per cent. In compensation, the automatic seizures increased from 11 to 37 per cent and the subjective seizures from 11 to 33 per cent. Presumably this finding has to do with the influence of age on the development of both the neurophysiology of the brain and the individual's psychological processes.

COMMENT

The following considerations support the thesis that psychomotor seizures may in most instances be a sequelae of injury to the brain—the frequent evidence of brain damage that antedated the epilepsy, the increased incidence of seizures with increased age and the frequent association with destructive grand mal instead of innocuous petit mal, plus the tendency of convulsions to precede the onset of the psychomotor variety. Antecedent injury is also suggested by the adversive and localizing nature of the symptoms, the frequency of spike foci in the electroencephalogram, and the lowered incidence of epilepsy among relatives compared with patients having other types of seizures. Besides being especially liable to trauma, portions of the temporal lobe, as Spielmeyer[19] pointed out, are exposed to sclerosis because of their unsatisfactory vascular supply.

SUMMARY

Based on clinical characteristics, the psychomotor (temporal) epilepsies were divided into three groups and eight subgroups. Seizures of 414 patients were distributed among the three groups as follows: psychomotor, 43 per cent; automatic, 32 per cent; and subjective (psychic), 25 per cent. The relative size of the automatic and subjective groups increased progressively with increasing age of patients.

Of 1,900 office patients, 20 per cent gave a history of psychomotor (temporal lobe) seizures. With increasing age of patients there was an increase in the incidence of psychomotor seizures (relative to other types) and an increase in the number of patients having both psychomotor and grand mal seizures. Sixty-three per cent of all psychomotor patients had a history of grand mal also, but only three per cent a history of petit mal. In the grand mal-psychomotor group, grand mal began a year or more before psychomotor seizures in 64 per cent, and a year or more after in 36 per cent. Acquired brain pathology antedated the onset of epilepsy in 33 per cent of patients having both convulsions and psychomotor

seizures, and in only 15 per cent of patients having only a member of the petit mal triad. The incidence of epilepsy among near relatives was 2.7 per cent for patients having psychomotor seizures (alone or associated with grand mal), but 5.4 per cent for those with a history of petit mal and grand mal.

These data suggest that psychomotor seizures may arise as a consequence of damage to a temporal lobe, possibly as a result of earlier convulsions, anoxia, trauma or infection.

REFERENCES

1. Lennox, W. G.: The petit mal epilepsies and their treatment with tridione, J. A. M. A. 129:1069, 1945.
2. Lennox, W. G.: A. Research Nerv. & Ment. Dis., Proc. (1946) 26: 1947.
3. Adams, F.: The Extant Works of Aretaeus, London, Sydenham Society, 1856.
4. Gaddesden, John of: Rosa Anglica, Pavia, 1492.
5. Bright, R.: Reports of Medical Cases, Vol. II, Part II, 1831.
6. Mead, R.: The Medical Works of Richard Mead, London, 1712.
7. Turner, W. A.: Epilepsy: A Study of the Idiopathic Diseases, New York, The Macmillan Company, 1907.
8. Wilson, K.: The epilepsies, in Bunke and Fourster: Handbuch der Neurologie, Berlin, Julius Springer, 1935.
9. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Cerebral dysrhythmias of epilepsy: Measures for their control, Arch. Neurol. & Psychiat. 39:298, 1938.
10. Maudsley, H.: Responsibility in Mental Disease, New York, D. Appleton & Co., 1874.
11. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield, Ill., Charles C Thomas, 1941.
12. Lennox, W. G.: Amnesia, Real and Feigned, Am. J. Psychiat. 99:732, 1943.
13. Stafford-Clark, D., and Taylor, F. H.: Clinical and Electroencephalographic Studies of Prisoners Charged with Murder, J. Neurol., Neurosurg. & Psychiat., 12: 325, 1949.
14. Lennox, W. G., and Davis, Jean: Clinical correlates of the fast and the slow spike-Wave EEG, J. Pediat. 5:626, 1950.
15. Spratling, W. P.: Epilepsy and its Treatment, New York, W. B. Saunders Company, 1904.
16. Lennox, W. G.: Psychology, psychiatry and seizures, Am. J. Orthopsychiat. 19:432, 1949.
17. Taylor, J.: Selected Writings of John Hughlings Jackson, London, Hodder and Stoughton, 1931.
18. Lennox, W. G.: Childhood Epilepsy, New York State J. Med. 50:2263, 1950.
19. Spielmeyer, W.: The anatomic substratum of the convulsive state, chapter XVI, in Epilepsy and the Convulsive States, Baltimore, Williams and Wilkins Co., 1931.

The obvious though mysterious connection between the brain and the mind—between the large mass of matter within the skull and our spiritual nature, has given rise to much investigation and controversy.

But many of the investigations and controversies relating to this subject, have not, I apprehend, been conducted in a right spirit, with the sole desire of ascertaining the exact truth, but oftener with a wish to establish, or to overthrow, some preconceived and frequently pre-advanced opinion.

—Amariah Brigham in *An Inquiry concerning the Diseases and Functions of the Brain, the Spinal Cord and the Nerves*, published in 1840.

Intracranial Neoplasm Associated with Fourteen and Six Per Second Positive Spikes

Wayland A. Stephenson, M.D.

THE clinical correlates of 14 and six per second positive spikes have been reported by Gibbs and Gibbs[1] who concluded that such spikes are of thalamic or hypothalamic origin. Such patterns have been encountered in this laboratory in 32 of 2500 adult patients. Relatively few of these cases showed evidence of organic neurologic disease. In the two patients who are the subject of this paper, neoplasms were verified at operation and the anatomic location was such as to afford some support to the thesis that the source of the positive spikes is in the diencephalon. For this reason the following cases are detailed.

Case 1.—W. M. C. aged 27 was admitted to the hospital on July 31, 1950 because of seizures with left-sided onset. There had been progressive weakness of the left arm since 1947 with difficulty in fine movements of the hand. In August 1949 and March 1950 the patient had had Jacksonian episodes beginning in the left arm followed by spread to the left face and the left lower extremity, after which generalized tonic and clonic seizures supervened. There was tongue biting and incontinence of urine and feces. Shortly before admission the patient had noticed blurring of vision and a numb sensation of the left side of the face. Physical examination was essentially negative except for the neurologic findings which consisted of marked paresis of the musculature of the left upper extremity, especially of the small hand muscles. There was drooping of the left side of the mouth and widening of the palpebral fissure. The left side of the face was questionably hypesthetic. The deep reflexes of the left arm and leg were decreased and there was a left Hoffmann sign. No sensory defect could be demonstrated over trunk and extremities and there was no weakness of the left leg. The spinal fluid pressure was normal, total protein was 18 mg. and there were no cells. Complement fixation test for syphilis was negative and the gold curve was flat. Blood count and urine analyses were within normal limits. Skull, chest, gastro-intestinal and flat abdominal films were normal. On the basis of the neurologic findings a clinical impression of a cortical lesion, probably neoplastic, in the right motor area for arm was made.

Electroencephalographic studies carried out on March 24, 1950, during both wake

From the electroencephalographic laboratory, Veterans Administration Hospital, Hines, Ill. Published with the approval of the chief medical director, Veterans Administration. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

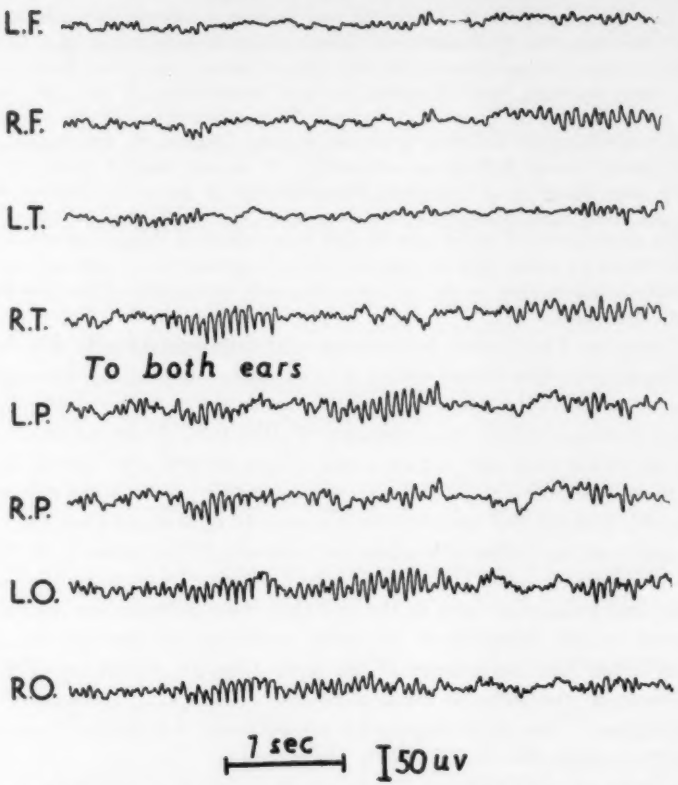


FIG. 1. Fourteen per second positive spikes have greatest amplitude in the right temporal derivation (Case 1).

and sleep with multiple leads over the suspected arm areas and using a variety of recording techniques, failed to demonstrate any abnormality or asymmetry. Radio isotope localization study performed on April 10 was reported as within normal limits and showed no evidence of tumor. Later a beginning papilledema was noted, and on April 19, 1950 ventriculography revealed downward displacement of the right lateral ventricle with some shift to the left and a filling defect of the middle portion. On April 21, 1950 isotope study following ventriculography revealed very slight but persistent differential concentration on the right near the midline, suggesting an organic lesion of very avascular type. A right osteoplastic craniotomy was performed on May 9, 1950, and a cystic neoplasm was found underlying the arm area, just anterior to the Rolandic vessels. The tumor was removed as far as the ependyma of the ventricle, and histological study revealed it to be a fibrillary astrocytoma. The patient was ambulatory one week postoperatively, although with greater left-sided weakness than before. Because of a postoperative seizure, bromides were prescribed, 0.5 gm. three times a

day. He was readmitted on November 10, 1950 because of recurrent left-sided seizures which were controlled by Dilantin and phenobarbital. Examination at that time revealed neurologic findings almost identical to the postoperative condition. Radio isotope study again showed a focus of slightly increased concentration in the right frontal area consistent with the presence of a tumor. During preparation of the patient for electroencephalographic recording a seizure occurred. Because of premonition of a second seizure sodium Amytal was administered. A tracing obtained during the succeeding sleep (figure 1) is exceedingly abnormal with 14 per second positive spikes appearing in the right temporal and to a lesser extent in the right occipital areas where at times six to seven per second patterns appear as a result of suppression of alternate waves. The 14 per second sleep spindles are of lower amplitude in the right parietal and occipital derivations than on the left, and some mild irregularity of the base-line is present on the right.

Comment: Electroencephalographic and isotope studies at first failed to demonstrate this tumor which proved to be subcortical. Incomplete removal was carried out as deeply as the ependyma and after eight months there was some evidence of progression. At that time (eight months later) sleep recording soon after a grand mal seizure showed very characteristic 14 per second positive spike discharges appearing on the right side from temporal, parietal and occipital derivations. It is believed that the positive spikes are an irritative response to extension of the tumor medially to the central gray masses. Of interest is the limitation of primary discharges to the right hemisphere despite the fact that these patterns are commonly bilateral, though independent, occurring sometimes on one side and then on the other. The asymmetry of the sleep spindles, which are of lower amplitude on the right, is usual in lesions interrupting thalamocortical connections.[2, 3] The slow frequencies are probably ascribable to surgical interference with the cortex and its blood supply.

Case 2.—A. P. D., a 28 year old white man, had had failing vision for four years and at the time of admission was almost blind in the left eye. There was history of occasional mild headache consisting of pain above the eyes for several years. He described himself as "less peppy" than normal, and complained of recent onset of polydipsia and polyuria. His weight had remained at 200 lbs. for several years, but somewhat above his previous level. There had been no changes in hair distribution or texture. He admitted some decrease in libido. Examination revealed a well developed, mildly lethargic, obese white man who was well oriented and cooperative but somewhat slow in answering questions. Sense of smell was preserved. The extra-ocular muscle movements were normal; the pupils were rather large and reacted both to light and in accommodation. The left optic disc was white and the right was essentially normal. There was some flattening of the right nasolabial fold, and pinprick was felt less well on the right side of the face than on the left. Corneal reflexes were normal. Motor power of the upper and lower extremities was normal; deep reflexes were brisk and symmetrical, and sensation over the trunk and extremities was normal. Ophthalmologic study revealed markedly reduced vision in the left eye, less so in the right eye, with an incomplete right homonymous hemianopsia. Basal metabolic rate was persistently

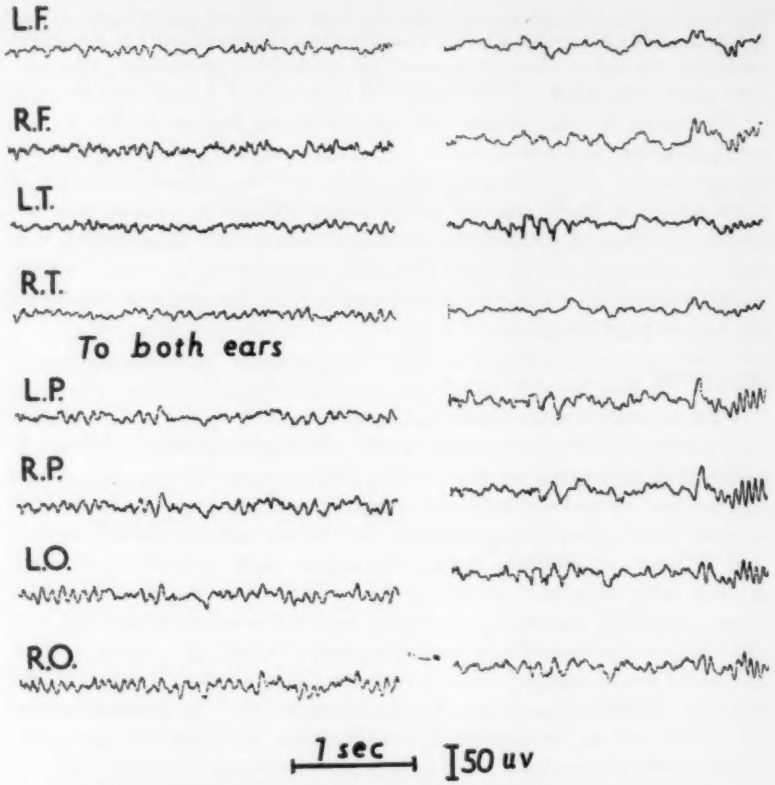


FIG. 2. Normal patterns recorded with the patient awake. Second portion shows six per second positive spikes with greatest amplitude in the left temporal (Case 2).

low, the lowest value being minus 23 per cent. X-ray study of the skull showed marked enlargement of the sella turcica with erosion of both clinoids. Blood and urine examinations were within normal limits in all respects, including urine specific gravity. Electroencephalographic study revealed rather low voltage patterns in the waking state with 10 per second frequencies predominant, especially in the occipital derivations. During drowsiness frontal and parietal leads showed some low amplitude fast frequencies. With the patient asleep several bursts of six per second positive spikes (figure 2) were recorded from the left hemisphere, especially the left temporal; one burst occurred also on the right side. Sleep spindles were well developed and symmetrical. A clinical diagnosis of chromophobe pituitary adenoma was made prior to operation. Endocrine replacement therapy was instituted, and on March 3, 1950 a right frontal craniotomy was performed. A tumor was disclosed which extended far beyond the confines of the sella, almost obliterating the optic chiasm and pressing upward into the third ventricle; it extended more to the left than to the right. There were many adhesions to surround-

ing structures, and during removal of portions of the lesion the patient's general condition became poor. The operation was terminated and he expired about 12 hours postoperatively. Permission was not granted for postmortem examination. Diagnosis: chromophobe adenoma of the pituitary.

Comment: In this patient the only abnormal feature of the electroencephalogram was the presence of six per second positive spike discharges during sleep. Symmetrical sleep spindles suggest integrity of thalamocortical fibers, and normal patterns during the waking state reveal no evidence of cortical dysfunction. It was noted at operation that there was invasion of the third ventricle. Such invasion would impinge on the diencephalic areas which are thought to be the origin of 14 and six per second positive spikes.

DISCUSSION

Patients with organic neurologic disease have constituted a rather small portion of our positive spike group. Although many had a history of head injury of varying severity, such a history is so common in patients referred for electroencephalographic study that its significance in the present series cannot be determined. Six patients showed definite neurologic findings. In addition to the two tumor cases detailed, there were patients with traumatic paraplegia and concomitant severe intracranial injury, multiple sclerosis, progressive cerebellar degeneration, and one with chronic polyneuritis of undetermined etiology. It would be premature to draw definite conclusions regarding the site of origin of the discharges in these cases, but in each instance, with the possible exception of the patient with cerebellar degeneration, structural changes probably occurred in the upper brain stem.

SUMMARY AND CONCLUSION

Two cases are reported, one with 14 per second positive spikes and one with six per second positive spikes, in patients with proved intracranial neoplasm. Each lesion was so placed as to involve the deep nuclear structures.

It is believed that these deep structures are the source of the 14 and six per second positive spikes.

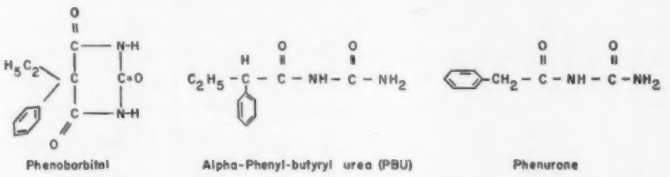
REFERENCES

1. Gibbs, F. A., and Gibbs, Erna L.: Electroencephalographic evidence of thalamic and hypothalamic epilepsy, Neurology 1:136, 1951.
2. Cress, C. H., and Gibbs, Erna L.: Electroencephalographic asymmetry during sleep in patients with vascular and traumatic hemiplegia, Dis. Nerv. System 9:327, 1948.
3. Epstein, Joseph A., and Lennox, Margaret A.: Electroencephalographic study of experimental cerebro-vascular occlusion, EEG & Clin. Neurophysiol. 1:491, 1949.

Anticonvulsant and Toxic Effects of Alpha-Phenyl-Butyryl Urea

Marshall J. Orloff, M.D., P. E. Feldman, M.D., Charles H. Shaiova, M.D. and Carl C. Pfeiffer, Ph.D., M.D.

THE effectiveness of alpha-phenyl acetylurea (Phenurone) in the treatment of psychomotor, petit mal and grand mal types of epilepsy and the occasional toxic side effects produced by this drug have been reported.[1-4] This study deals with alpha-phenyl-butyryl urea (PBU), which is the ethyl analogue of Phenurone and the aliphatic analogue of phenobarbital. The chemical formulas are as follows:



Since PBU is a close chemical cogener of two clinically effective anticonvulsants, a careful laboratory and clinical study was instituted.

LABORATORY RESULTS

Toxicity. In the mouse, the minimal toxic dose of PBU was found to be 150 mg./kg. by the intraperitoneal route. The general effect of the drug was central nervous system depression. In the dog, 250 mg./kg. orally produced no toxic effects. The oral administration of 500 mg./kg. produced slight ataxia of 30 minutes duration, and 1.14 gm./kg. orally produced vomiting and slight ataxia which lasted for only two hours. Daily oral doses of 200 mg./kg. were given to a group of mice for three weeks and no toxic effects were noted.

From the department of pharmacology, University of Illinois, and the Manteno State Hospital, Manteno, Illinois.

Read before Cleveland meetings of the American Society for Pharmacology and Experimental Therapeutics, March, 1951.

TABLE 1

COMPARATIVE EFFECTS OF PBU AND SOME COMMON ANTICONVULSANTS AGAINST ELECTROSHOCK, METRAZOL AND STRYCHNINE IN MICE

Drug	*I.P. Dose mg/kg*	*Side Effects*	*Testing Interval*	*Electroshock Protection (Multiples of threshold shock)*	*Type of Seizure*
PBU	200	Moderate depression, ataxia, and hind limb weakness	2 hr.	9X	Modified—Tonic flexor
Dilantin	100	Moderate ataxia and hyperactivity	1½ hr.	9X	Modified—Clonic
Phenurone	300	Slight depression and ataxia	2 hr.	9X	Modified—Tonic flexor

				Metrazol Thresholds—% Elevation*				
				First Twitch	*Pseudoconvulsion*	*Persistent Convulsion*	*Type of Seizure*	*Mortality %*
PBU	200	Moderate depression, ataxia, and hind limb weakness	1½ hr.	—32	—20	66	Clonic	10
Tridione	400	Moderate depression and ataxia	1 hr.	114	126	62	Tonic, flex.-ext.	100
	500	Marked depression and ataxia	1½ hr.	136	137	67	Tonic, flex.-ext.	100
Phenurone	400	Marked depression and ataxia	1½ hr.	129	160	83	Clonic	30

				*Strychnine Threshold**—% Elevation*	*Mortality—%*
PBU	200	Moderate depression, ataxia, and hind limb weakness	1½ hr.	92	85
Phenobarbital	50	Marked depression and ataxia	2 hr.	50	65
Phenurone	400	Marked depression and ataxia	1½ hr.	50	60

*Timed intravenous infusion of 0.5% metrazol

**Timed intravenous infusion of 0.01% strychnine

Anticonvulsant activity. The anticonvulsant potency of PBU was evaluated in mice on the basis of four tests: 1) modification of supramaximal electroshock convulsions, 2) elevation of the threshold for Metrazol-induced seizures, 3) elevation of the threshold for strychnine-induced seizures, and 4) elevation of the threshold for ammonium-induced convulsions.

Electroshock convulsions were induced by the use of an alternating current stimulator with a stimulus duration of 0.3 second. The stimulus was applied by means of eye electrodes.[5] Anticonvulsant potency was measured in terms of the multiples of the threshold stimulus necessary to produce an unmodified convulsion. (The convulsion threshold for electroshock in the mouse had been previously determined in a large series of control animals.) The largest shock (in milliamperes) which this stimulator can deliver is nine times the threshold shock; therefore, a drug is considered to be of highest potency if it modifies the convulsions when a shock nine times the threshold shock is given.

Metrazol and strychnine convulsions were induced by the timed intravenous infusion method, and the ability of the drug to elevate these thresholds was used as a measure of anticonvulsant potency.[6]

Ammonium ion convulsions were induced by the timed intravenous infusion of a 5 per cent solution of ammonium acetate at the rate of 0.05 cc. every 10 seconds, and the increase in the amount of ammonium acetate necessary to produce a tonic extensor convulsion was used as an index of anticonvulsant activity.

TABLE 2

EFFECTS OF PBU AGAINST AMMONIUM-INDUCED CONVULSIONS*[7]

Drug	*Oral Minimal Toxic Dose mg/kg*	*% Elevation of Threshold at M.T.D.*	*50% Elevation Dose mg/kg*	*Ratio M.T.D./ 50% Elevation Dose*
PBU	150	69	93	1.61
Mesantoin	75	42	89.5	.84
Phenurone	175	37.5	224.5	.78
Dilantin	50	47.2	67.5	.74
Phenobarbital	40	22	73	.55

*Timed intravenous infusion of 5% ammonium acetate.

The results obtained with PBU in these four tests and a comparison of this drug with some clinically effective anti-epileptics are shown in tables 1 and 2. PBU effectively protected the animals against convulsions induced by electroshock, strychnine and ammonium, and compared very favorably with other anticonvulsants. PBU failed to elevate the Metrazol

thresholds, although it markedly modified the Metrazol convulsions and protected the animals from death. Clinical trials with this drug were, therefore, instituted in various types of epileptic disorders.

CLINICAL RESULTS

PBU was tested on a group of 10 institutionalized epileptic patients. Five cases were diagnosed as grand mal epilepsy, four cases as grand mal plus psychomotor epilepsy, and one case as grand mal plus petit mal epilepsy. Diagnoses were made on the basis of electroencephalographic evidence, observations of seizures over long periods of time and extensive investigations of the case histories. All of the patients had severe epilepsy, and most of them had frequent seizures which had never been completely controlled by previous routine medication. The routine medication consisted of phenobarbital 300 mg. and Dilantin 300 mg. daily and was discontinued during the PBU treatment periods. The testing periods varied from four days to 103 days, and the doses of PBU varied from 1.2 gm. per day to 7.2 gm. per day. During the testing periods, the patients were seen by one of us daily. In addition, they were under constant observation by a group of special attendants assigned for this task. A brief summary of each of the cases follows.

CASE SUMMARIES

Case 1.—C. K., a 34 year old female

Diagnosis—idiopathic epilepsy, grand mal and psychomotor
Unmedicated seizure frequency—grand mal, 12 to 16 per month
psychomotor, infrequent
Frequency on PBU—
8 days—1.2 gm. per day—two "light" seizures and one grand mal—patient developed status epilepticus on the eighth day of therapy
Side effects—none
Comment—At this dose, PBU failed to control seizures.

Case 2.—L. L., a 34 year old female

Diagnosis—idiopathic epilepsy, grand mal and psychomotor
Unmedicated seizure frequency—grand mal, 4 to 5 per month (all seizures occur within seven days before or after onset of menses)
psychomotor, frequency unknown
Frequency on PBU—
42 days—1.2 gm. per day—ten "light" seizures (all but two occurred within seven days before or after onset of menses)
17 days—1.6 gm. per day—17 "light" seizures (all occurred within seven days before or after onset of menses)
8 days—2 gm. per day—four "light" seizures (all occurred within seven days before or after onset of menses)

Side effects—patient complained of weakness on two days, while taking 1.6 gm. per day of PBU.

Comment—On 1.2 gm. per day and 1.6 gm. per day the seizure frequency was increased. No conclusions can be drawn from the 2 gm. per day therapy because of the brief trial period. It is interesting to note that she had no grand mal attacks while on PBU therapy. All "light" seizures consisted of rolling on the floor, moaning and picking at her clothes, with no tonus or clonus. These may represent modified grand mal seizures (due to PBU), or they may be psychomotor attacks, the frequency of which was increased by PBU.

Case 3.—M. A., a 35 year old male

Diagnosis—idiopathic epilepsy, grand mal; alcoholism

Unmedicated seizure frequency—grand mal, one per month, if he abstains from alcohol

Frequency on Dilantin and phenobarbital (300 mg. of each daily)—grand mal, two per year

Frequency on PBU—

39 days—1.5 gm. per day—two grand mal

64 days—2 gm. per day—one grand mal, one modified grand mal

Side effects—none

Comment—at this dose, PBU neither increased nor decreased the seizure frequency.

Case 4.—H. W., a 46 year old female

Diagnosis—idiopathic epilepsy, grand mal

Unmedicated seizure frequency—grand mal, three per month

Frequency on Dilantin and phenobarbital (300 mg. of each daily)—grand mal, one per month

Frequency on PBU—

9 days—2 gm. per day—one grand mal, one modified grand mal

Side effects—On four of the nine days she experienced pain in the abdomen and vomiting, apparently a PBU-induced gastritis. On one day she had a headache.

Comment—During this brief trial, PBU did not reduce seizure frequency. The only toxic effect at this dose was gastritis.

Case 5.—R. V., a 20 year old male

Diagnosis—idiopathic epilepsy, grand mal and psychomotor

Unmedicated seizure frequency—grand mal, 4 to 8 per month; psychomotor, frequency unknown

Frequency on Dilantin and phenobarbital (300 mg. of each daily)—grand mal, 3-8 per month; psychomotor, 3-8 per month

Frequency on PBU—

15 days—2 gm. per day—four psychomotor
one grand mal

7 days—2.4 gm. per day—three psychomotor

Side effects—Nine of the 22 days of therapy were complicated by abdominal cramps with or without anorexia, apparently due to gastric irritation. These symptoms decreased when the drug was given with meals.

Comment—PBU effectively controlled the grand mal attacks, but the frequency

of the psychomotor seizures remained the same or was increased slightly. The only toxic effect at this dose was gastritis.

Case 6.—E. H., a 28 year old male

Diagnosis—symptomatic epilepsy (central nervous system syphilis), grand mal and psychomotor

Unmedicated seizure frequency—grand mal, 10 to 60 per month
psychomotor, rare

Frequency on Dilantin and phenobarbital (300 mg. of each daily)—grand mal, 10 to 18 per month; psychomotor, rare

Frequency on PBU—

2 days—2 gm. per day—one modified grand mal

1 day—2.8 gm. per day—no seizures

6 days—3.2 gm. per day—one modified grand mal

Side effects—On the eighth day of therapy (fifth day of 3.2 gm. per day), the patient developed weakness and ataxia which progressed so that therapy was discontinued on the tenth day, after which he recovered rapidly.

Comment—From this brief trial no conclusions can be drawn, although grand mal seizures appeared to be modified and less severe. However, 3.2 gm. per day produced toxic effects.

Case 7.—N. B., a 53 year old female

Diagnosis—idiopathic epilepsy, grand mal

Unmedicated seizure frequency—grand mal, 30 per month

Frequency on phenobarbital (300 mg. daily)—grand mal, 12 to 16 per month

Frequency on PBU—

26 days—1.6 gm. per day—five grand mal

13 days—3.2 gm. per day—two grand mal

Side effects—On the tenth day of 3.2 gm. per day therapy the patient developed weakness and ataxia. On the eleventh day she was sent to the acute hospital with a temperature of 103.4° F. rectally, disorientation, inability to swallow, extreme restlessness, "athetoid" movements and retention of urine. By the thirteenth day, after two days of penicillin therapy, her temperature was normal, but the other symptoms persisted and in addition she became dehydrated. PBU was stopped on the fourteenth day. By the twentieth day the only remaining symptoms were stupor and urine retention, and by the thirtieth day (sixteen days after cessation of PBU therapy) she was alert and was easily fed.

Comment—PBU was very effective in controlling the grand mal attacks. However, the dose of 3.2 gm. per day was extremely toxic, apparently to the central nervous system. It is difficult to say how many of her symptoms were due to PBU, especially since her fever responded rapidly to penicillin, which indicated a superimposed infection.

Case 8.—G. C., a 36 year old male

Diagnosis—idiopathic epilepsy, grand mal

Unmedicated seizure frequency—unknown

Frequency on Dilantin and phenobarbital (300 mg. of each daily)—grand mal, nine per month (patient has frequent bouts of status epilepticus which are very difficult to control)

Frequency on PBU—Patient was sent to us in mild status epilepticus, after having just recovered from a period of status. The results were as follows:

1st day—1.2 gm. PBU—six grand mal

2nd day—5.2 gm. PBU plus 11.5 grains sodium Amytal intravenously—six grand mal

3rd day—7.2 gm. PBU—no seizures

4th to 7th days—6.4 gm. PBU per day—no seizures

8th to 9th days—5.6 gm. PBU per day—one grand mal

Side effects—On the fifth day of therapy he was very weak and complained of dizziness. By the sixth day he was quite ataxic, and on the seventh day became very restless and disoriented. On the ninth day the restlessness became extreme, and he developed dehydration, anorexia and vomiting; PBU was discontinued. On the eleventh day (two days after withdrawal) his condition was unchanged and in addition he developed an inflamed pharynx and a sore tongue, with a rectal temperature of 103.2° F. The fever responded to penicillin and antipyretic therapy. By the fourth day (after cessation of therapy) all of the symptoms had disappeared except the sore tongue and throat, and he appeared well.

A blood study performed at the height of toxicity (seventh day) gave normal results.

Comment—Although PBU was effective in controlling status epilepticus, the dose necessary to accomplish this was high and was extremely toxic to the central nervous system. Note the similarity of symptoms to case 7.

Case 9.—D. S., a 37 year old female

Diagnosis—idiopathic epilepsy, grand mal and petit mal

Unmedicated seizure frequency—unknown

Frequency on Dilantin (300 mg. daily) and phenobarbital (200 mg. daily)—grand mal, five to seven per month; petit mal, eight per month

Frequency on PBU—

1 day—2.4 gm. per day—two petit mal

7 days—3.2 gm. per day—one grand mal

4 days—3.6 gm. per day—no seizures

Side effects—On the seventh day of therapy (sixth day of 3.2 gm. per day) she developed weakness and ataxia. Disorientation was added on the eighth day, and by the twelfth day all of these symptoms increased and in addition she became extremely restless. PBU was stopped on the twelfth day. Two days after withdrawal of PBU the above symptoms were more severe and in addition she developed vomiting and anorexia. Three days after withdrawal she was dehydrated and had a rectal temperature of 101.8° F. which went up to 105° F. on the next day. The fever responded rapidly to penicillin and parenteral fluids. By the eleventh day after withdrawal she was greatly improved and by the eighteenth day she was up and about.

A blood study on the twelfth day of therapy revealed no abnormality. This was repeated on the seventh day after withdrawal with no change except for a hemoglobin level of 69 per cent. On the fifth day after withdrawal the nonprotein nitrogen was 37 mg. per cent and blood glucose was 150 mg. per cent.

Comment—Although PBU was effective in controlling seizures during this brief

trial, it was extremely toxic to the central nervous system. Note similarity of symptoms to case 7 and case 8.

Case 10.—B. I., a 31 year old male

Diagnosis—idiopathic epilepsy, grand mal

Unmedicated seizure frequency—grand mal, seven per day

Frequency on Dilantin and phenobarbital (300 mg. of each daily)—grand mal, four to seven per month; 15 periods of status epilepticus per year

Frequency on PBU—

4 days—4.8 gm. per day—one modified grand mal

Side effects—On the third day he developed ataxia and disorientation, and on the fourth day he developed extreme restlessness (athetoid movements), extreme weakness and difficulty in swallowing. On the fifth day, withdrawal of PBU was started and by the eighth day (three days after withdrawal) he had recovered.

Comment—PBU appeared to be effective in controlling seizures during this very brief and inadequate trial. However, it was extremely toxic and produced symptoms similar to those in cases 7, 8 and 9.

SIDE EFFECTS

PBU was extremely toxic at effective therapeutic dosage levels. The minimal toxic dose was between 2 gm. per day and 2.4 gm. per day, at which dose abdominal cramps, vomiting and anorexia occurred, apparently due to gastric irritation. These symptoms were reduced by administering the drug with meals.

At 3.2 gm. per day, extreme weakness and ataxia occurred after five to 10 days of therapy, sometimes accompanied by dizziness. These initial symptoms progressed and difficulty in swallowing, disorientation, extreme restlessness and athetoid movements resulted. Later dehydration and hyperthermia developed, possibly due to PBU, although inadequate feeding or secondary infection could have been responsible. One case developed urinary retention, one case developed an inflamed pharynx and sore tongue, and one case developed diarrhea plus a reduction in hemoglobin in addition to the aforementioned symptoms.

All cases recovered with no residual effects. The time necessary for complete recovery varied from three to 18 days after withdrawal of the drug, depending to some extent on the severity of symptoms.

It is interesting to note the similarity in man of some of the side effects produced by Phenurone to those produced by its analogue, PBU. Both drugs cause weakness and anorexia. Phenurone is reported to produce insomnia, while PBU produces extreme restlessness. Finally, the extreme disorientation seen in patients receiving PBU is vaguely similar to the reported psychotic manifestations in some patients receiving Phenurone. It should be stated, however, that the percentage of patients reported to

exhibit toxic effects from Phenurone is very much lower than the percentage to whom PBU was toxic.

SUMMARY AND CONCLUSIONS

Alpha-phenyl-butyryl urea (PBU), the ethyl analogue of Phenurone and the aliphatic analogue of phenobarbital, was found to be a potent anticonvulsant against artificially induced convulsions in laboratory animals. Further, it was found to be chronically non-toxic in effective doses.

In a group of 10 institutionalized patients with severe epilepsy, this drug appeared to be effective in controlling grand mal seizures. However, the drug produced severe toxic effects when doses necessary to bring about adequate control were given. PBU was not given an adequate trial in psychomotor epilepsy, but from the evidence now available it appears that the drug increases the frequency of psychomotor attacks. PBU was not tested in petit mal epilepsy. The extreme toxicity of alpha-phenyl-butyryl urea at effective anticonvulsant dosage levels precludes its use as a therapeutic agent in the treatment of epilepsy.

REFERENCES

1. Gibbs, F. A.; Everett, G. M., and Richards, R. K.: Phenurone in epilepsy, Dis. Nerv. System 10:47, 1949.
2. Abbott, J. A., and Schwab, R. S.: The serious side effects of the newer antiepileptic drugs: Their control and prevention. New England J. Med. 242:943, 1950.
3. Keith, H. M.: The use of phenurone for convulsive disorders of children: Preliminary report, Proc. Staff Meet., Mayo Clin. 25: 594, 1950.
4. Livingston, S., and Kajdi, L.: Use of phenurone in treatment of epilepsy, J. Pediat. 36:159, 1950.
5. Lanphier, E. H.: The Evaluation of Antiepileptic Drugs by Laboratory Methods, Thesis for M.S. Degree, Univ. of Illinois, 1949.
6. Orloff, M. J.; Williams, H. L., and Pfeiffer, C. C.: Timed intravenous infusion of metrazol and strychnine for testing anticonvulsant drugs, Proc. Soc. Exper. Biol. and Med. 70:254, 1949.
7. Jenney, E. H.: Personal communication.

A short time since I instituted, at the New York State Hospital for Diseases of the Nervous System, a series of experiments with the chloride of sodium in the treatment of epilepsy, but, although the salt was given in large doses, it produced no marked effect. I was led to these investigations by the facts that the bromide of potassium, the bromide of sodium, and the chloride of potassium, had been employed with success, and I thought there was sufficient analogy to warrant the hope that the chloride of sodium might prove beneficial.

—William A. Hammond in *A Treatise of Diseases of the Nervous System*, published in 1871.

Extradural Hematoma of the Posterior Fossa

Richard C. Schneider, M.D., Edgar A. Kahn, M.D. and Elizabeth Caroline Crosby, Ph.D., Sc.D.

EXTRADURAL hematoma confined to the posterior fossa, the so-called extradural cerebellar hematoma, is a rare clinical entity. As a rule this lesion has been overlooked because of the paucity of neurologic signs and symptoms or diagnosed so late that operation was of no avail. To date we have found only seven such cases in the literature which were diagnosed and successfully operated upon. Another case which was cured is reported here, and a discussion of the anatomic basis of one of its interesting neurologic findings is presented.

The scarcity of extradural hematomas limited to the posterior fossa is apparent when several large series of head injuries with extradural hemorrhage are examined.[8, 10, 12, 13, 14, 15, 16, 19] Of a total of 367 cases there were only two patients in whom the lesion was found confined to the posterior fossa, an incidence of 0.5 per cent of all extradural hemorrhages. One of these was presented by McKenzie[13] and is believed to be the first case of extradural cerebellar hematoma reported in the literature. The second case was noted by Munro and Maltby.[14] In both instances the patients succumbed and the clot was found at postmortem examination.

Isolated cases in which this lesion was found, operated upon and the clot successfully removed have been reported by Anderson,[1] Coleman and Thomson,[2] Kessel,[11] Scoville,[17] Turnbull[18] and Watts.[20] A case reported by Fleminger and Smith,[5] which has previously been overlooked in reviewing the subject, should be included in this group. The latter was reported as a case of acholasia of the esophagus following depressed fracture of the base of the skull. In addition, the patient exhibited a modified Collet's syndrome, and at operation an extradural hematoma of the posterior fossa was found. The clot was evacuated, and the patient recovered completely after a prolonged convalescence.

From the department of surgery, section of neurosurgery, and department of anatomy, section of neuroanatomy, University of Michigan Medical School, Ann Arbor, Michigan.

It may seem unnecessary to separate the cases of extradural hemorrhage confined purely to the posterior fossa from those in which the clot overlies both the occipital and cerebellar regions. In the latter instance it is usually impossible to determine whether the lesion originated below the lateral sinus and dissected upward to the occipital pole, or whether it was primary above the sinus and drained downward into the posterior fossa. Differentiation between the locations of these lesions seems desirable because of some variations in neurologic signs and the ultimate prognosis.

Combined lesions of the posterior fossa and occipital region observed at autopsy have been reported by Lecount and Apfelbach,[12] Vance,[16] Gordy[6] and Herren.[9] The latter author also presented a case which was operated upon but succumbed a short time later. McKenzie[13] in his original report lists two patients with whom he had a similar experience. Gurdjian and Webster[8] and Grant and Austin[7] successfully operated upon lesions which overlay both the posterior fossa and the occipital areas, and in both instances the individuals recovered completely.

CASE REPORT

On March 5, 1950, a 43 year old white female fell in the bathtub striking her head. She suffered a stellate scalp laceration over the external occipital protuberance and was unconscious. After regaining consciousness at the local hospital four hours later, she complained of blurring of vision, dizziness, vague sensations and difficulty in coordinating her eye movements. A lumbar puncture performed by her own physician was reported as showing a spinal fluid under normal pressure with six white blood cells and 460 red blood cells per high powered field. The Pandy test was one plus. X-rays of the skull showed no evidence of fracture. Four days later the patient had two episodes of projectile vomiting and complained of severe occipital headache. On the following day the patient was admitted to University Hospital, at which time she was sufficiently alert to give the above history. She complained of headache, difficulty in talking and swallowing, and experienced numbness in the right hand. The patient, an extremely intelligent woman, commented that her speech was like "someone who had multiple sclerosis."

Examination showed blood pressure 120/90, pulse 82, respirations 18, temperature 99.2°. There was a minimal amount of purulent drainage from an undebrided stellate laceration over the external occipital protruberance. The patient was lethargic, but well oriented and had a tendency to lie on her right side. Pupils were equal, reacting to light and accommodation, and there was questionable blurring of the nasal margins of the optic discs. The tongue deviated slightly to the right, but the remainder of the cranial nerves were normal. No motor weakness was observed, but there was definite ataxia on finger to nose test with pronounced dysdiadokokinesis on the left side. She stood on a wide base and fell backward even with the eyes open. Nystagmus was seen on left lateral gaze (rapid component to the left). Deep reflexes were hyperactive in the right arm and in both lower extremities, but there were no pathologic reflexes. A diagnosis of intracranial hemorrhage of the posterior fossa was made and the patient was scheduled for trephination.

On March 11, 1950 a left suboccipital craniotomy was performed with evacuation of a large extradural hematoma from the left posterior fossa. The dura on the left side was depressed about three or four centimeters by the clot. The hematoma, which was largest and most adherent just below the left lateral sinus, could be scraped away. Immediately after irrigation the dura pulsated freely. No membrane or fracture was noted. Because of the proximity to the infected midline stellate scalp laceration, closure of the wound was performed with through and through black silk mattress sutures without drainage. A trephine hole was then made about two or three centimeters above the left lateral sinus to rule out the possibility that the clot had extended upward over the hemisphere. No hematoma was found. The dura, which pulsated freely, was not opened either at the trephine hole or at the craniectomy wound for fear of contamination from the purulent midline stellate laceration. Closure was carried out with black silk mattress sutures and a collodion dressing applied. The laceration was then completely excised and packed open with a Metaphen in oil dressing. Postoperatively the patient received sulfadiazene, one gm. every four hours, with an equal dosage of sodium bicarbonate, and regular penicillin 100,000 units intramuscularly every three hours.

On the following morning the patient was alert and no longer dizzy. Ataxia on left finger to nose test began to diminish, so that within twenty-four hours it had almost disappeared. There was no further difficulty with talking or swallowing. Nystagmus was now present on right lateral gaze (rapid component to the right), i.e. in the direction opposite to that observed at admission. Within two or three days this sign vanished completely. On March 17 the pack was removed from the midline suboccipital wound and a through and through closure was carried out with No. 30 steel wire sutures. The wounds healed nicely. Sutures were removed from the craniectomy wound on the seventh postoperative day and from the secondary closure on March 22, the day of discharge. At that time the patient was neurologically negative, and upon follow-up examination four months later she was asymptomatic and in excellent condition.

DISCUSSION

Coleman and Thomson,[2] in reporting the first case of closed extradural cerebellar hematoma which was successfully operated upon, presented the following diagnostic criteria for such a lesion: "There is a history of a blow upon the back of the head severe enough to produce a fracture of the skull, but which may cause unconsciousness. This is followed by headache of gradually increasing severity and is usually accompanied by nausea and vomiting. Drowsiness and restlessness appear and progress until the patient lapses into unconsciousness. However, during the drowsy state several things may be noted. The patient prefers to lie on one side and will promptly return to the same side when placed upon his back. Nuchal rigidity develops, nystagmus may or may not be present, and the deep reflexes disappear. As unconsciousness deepens, generalized hypotonia develops, the pulse and respirations become irregular, and death is imminent unless there is prompt surgical intervention with removal of the clot."

Since then, other articles have been written attempting to correlate the signs and symptoms into a syndrome, but there has been no one definite picture common to all cases. The single important factor in making the diagnosis of extradural hematoma of the posterior fossa is a high index of suspicion that such a lesion may exist. Our case had a course somewhat similar to that described by Coleman and Thomson. When there is nystagmus on extreme lateral gaze, ataxia, hypotonia, hyporeflexia or a cerebellar fit, or if there is a compound fracture in the region of the posterior fossa, the diagnosis is obvious. However, in many cases the patient is so deeply comatose that accurate evaluation of neurologic signs is impossible, and we must resort to objective findings to suggest the presence of this lesion.

The case presented in this article is one of the few that did not have a skull fracture, but such a finding in the occipital region lends support to the diagnosis of an extradural hematoma of the posterior fossa. Our patient had a midline occipital scalp laceration, and Gordy[6] has emphasized that such a finding suggests an underlying lesion. If such an occipital fracture and a contusion or laceration of the scalp is observed in a patient who has remained unconscious or is becoming progressively more comatose, and in whom this state of unconsciousness cannot be attributed to a supratentorial lesion, the authors believe that there is sufficient evidence to warrant trephination over the posterior fossa for a suspected hematoma. If one waits for changes in the blood pressure, pulse, or respirations, the patient may die a respiratory death before operation can be performed. Anderson[1] in reviewing the literature on the subject indicates that when attention is directed to the posterior fossa and operation is performed with evacuation of an extradural hematoma, 75 to 100 per cent of the cases have an excellent chance of recovery. Neurologic surgeons do not hesitate to trephine the temporal region of a patient with a head injury who has a fracture line extending through the middle meningeal groove and an increase in depth of state of consciousness. We believe that there should be little hesitancy in trephining the posterior fossa of a similar type of patient who has sustained a fracture of the occipital bone extending downward through the foramen magnum even without neurologic signs referable to that area. This may aid in reducing the mortality rate. Lumbar puncture[2] adds little to the diagnosis and is probably dangerous, due to the possibility of development of a foramen magnum pressure cone.

The lateral sinus and the torcular herophili are the most common sources of extradural bleeding in the occipital and suboccipital regions. In the first case report on extradural hematoma of the posterior fossa, McKenzie[13] suggested that if an occipital lobe extradural clot is dis-

covered at trephination, another burr hole should be made in the suboccipital region to rule out extension of the hematoma downward into the posterior fossa. The converse is also true if a clot is found initially in the posterior fossa. Both types of cases should be trephined above and below the sinus. When the literature is reviewed and the number of cases with lesions in both locations is noted, one realizes that McKenzie's point should be emphasized.

We have stated previously that it is probably advisable to differentiate the extradural hematomas confined to the posterior fossa from those cases in which there was in addition a clot in the occipital region. Several of the cases having the combined lesion had anisiocoria, hemiparesis and pyramidal tract signs which were usually not seen in the lesions limited to the posterior fossa. In addition, it is interesting to observe that to date all of the reported cases which were operated upon and found to have an extradural hematoma confined to the posterior fossa have survived. The prognosis is, therefore, better in this type of lesion, possibly because the less extensive clot has not caused irreversible physiologic damage.

COMMENT ON NYSTAGMUS

The nystagmus observed in our case merits further discussion. Preoperatively our patient had nystagmus with the rapid component toward the left on extreme left lateral gaze, the side on which the greater portion of the clot was located. However, examination on the morning following operation revealed that when the gaze was toward the extreme right the nystagmus had switched toward the right, or the side opposite that from which the hematoma had been removed. In two or three days this symptom completely disappeared. Nystagmus on extreme lateral gaze suggests a cerebellar (or inferior cerebellar peduncle) involvement.

One of us[4] had evolved the hypothesis that the pyramis of the cerebellum indirectly exerts a regulatory influence over the contralateral vestibular nuclei with a pronounced effect upon nystagmus. More recently Cranmer[3] has shown experimentally that this hypothesis is correct in the monkey, and upon discussing our case with him we have found that the clinical pattern in our patient coincides with his experimental findings on nystagmus.

According to this work the pyramis seems to be an important reflex center. There is a voluntary control exerted upon the homolateral pyramis by the frontopontine tract (figure 1). The latter starts in the cortex of the frontal lobe and extends as a frontopontine tract through the frontal portion of the internal capsule, the basis pedunclui, and finally terminates in the homolateral pontine gray (not labeled). Here synapse occurs and

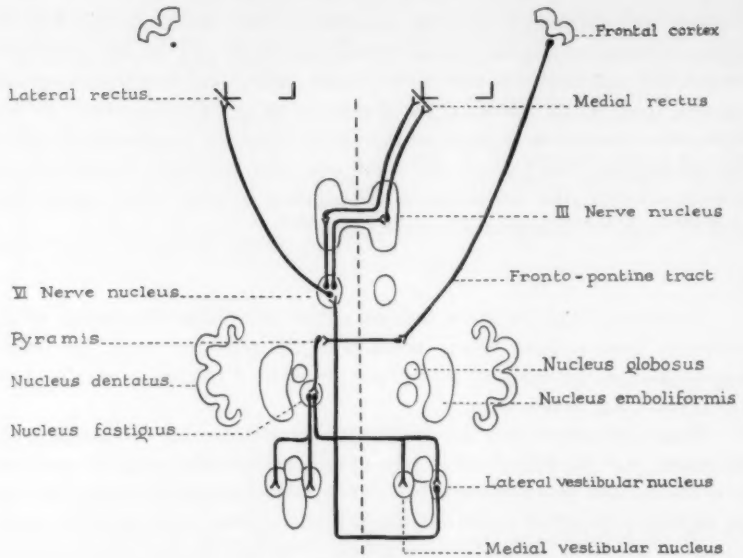


FIGURE 1

fibers traverse the brachium pontis to project upon the contralateral pyramis. The latter exerts an inhibitory reflex control upon the nucleus fastigius, which in turn inhibits the contralateral medial and lateral vestibular nuclei. After synapse another fiber leaves the lateral vestibular nucleus and crosses back to join the medial longitudinal fasciculus extending forward to the abducens complex (abducens nucleus and parabducens nucleus) on the same side as the controlling pyramis and nucleus fastigius. From the abducens nucleus, fibers run to the homolateral rectus muscle. The small celled portion of the abducens complex (the parabducens) discharges through the medial longitudinal fasciculus to the nucleus of Perlia. Synapse occurs and fibers proceed to the medial rectus muscle of the opposite side so that conjugate deviation is maintained.

In the case presented here voluntary control by the frontopontine tract may be completely disregarded because the extradural hematoma exerted pressure directly on the left cerebellar cortex, the pyramis. Ordinarily the vestibular nuclei are maintained in equilibrium, but when the left pyramis was compressed by clot, the primary inhibitory effect which it has upon the homolateral nucleus fastigius was removed, thereby causing the nucleus fastigius to produce an even greater inhibitory effect upon the contralateral vestibular nuclei. As a result, the right lateral vestibular

nucleus was suppressed and the impulses to the left abducens and the right oculomotor nuclei caused nystagmus with the rapid component to the left and the slow one to the right. After the hematoma was removed, there was a tendency for overswing to occur temporarily so that there was a complete reversal of this cycle. Now the rapid component of the nystagmus was toward the right side and the slow to the left. As edema subsided the vestibular nuclei again recovered their equilibrium and nystagmus disappeared completely.

SUMMARY

A review of the literature indicates that extradural hematoma of the posterior fossa is rare. When confined to the posterior fossa the neurologic signs may be different from those observed if the lesion overlies both the occiput and cerebellum.

Since a definite syndrome cannot be relied upon for establishing the diagnosis, one must frequently rely upon objective findings. A contusion over the occiput plus a fracture line in this region, in a patient who has had an increased depth of unconsciousness and no other evidence of a supratentorial lesion, is sufficient to warrant trephination over the posterior fossa. If operated upon, the prognosis is excellent provided that the lesion is limited to the posterior fossa.

An explanation of the nystagmus in this case may be found if it is compared with the experimental work in the monkey performed by Cranmer.

REFERENCES

1. Anderson, F. M.: Extradural cerebellar hemorrhage: Review of the subject and report of a case, J. Neurosurg. 6:191, 1949.
2. Coleman, C. C., and Thomson, J. L.: Extradural hemorrhage in the posterior fossa, Surgery 10:985, 1941.
3. Cranmer, L. R.: Nystagmus of the central vestibular apparatus and cerebellum, Ann. Otol., Rhin. & Laryng., to be published.
4. Crosby, E. C.: The application of neuroatomical data to the diagnosis of selected neurosurgical and neurological cases, J. Neurosurg. 7:566, 1950.
5. Fleminger, J. J., and Smith, M. C.: Acholasia of oesophagus following depressed fracture of the base of the skull, Lancet 1:381, 1946.
6. Gordy, P. G.: Extradural hemorrhage of the anterior and posterior fossae, J. Neurosurg. 5:294, 1948.
7. Grant, F. D., and Austin, G. M.: Evacuation of traumatic extradural hemorrhage from the posterior fossa, Ann. Surg. 130: 963, 1949.
8. Gurdjian, E. S., and Webster, J. E.: Collective review of the literature and report of 30 cases of middle meningeal and 4 cases of dural sinus hemorrhage treated surgically, Internat. Abstr. Surg. 75:206, 1942.
9. Herren, R. Y., and Zeller, W. E.: Extradural hemorrhage of the posterior fossa, Arch. Surg. 60:953, 1950.
10. Kennedy, F., and Wortis, H.: "Acute" subdural hematoma and acute epidural hemorrhage: A study of seventy-two cases of hematoma and seventeen cases of hemorrhage, Surg., Gynec. & Obst. 63:732, 1936.
11. Kessel, F. K.: Cerebellar extradural hematoma, J. Neurol. & Psychiat. 5:96, 1942.
12. Lecount, E. R., and Apfelbach, C. W.:

Pathological anatomy of traumatic fractures of cranial bones and concomitant brain injuries, J. A. M. A. 74:501, 1920.
13. McKenzie, K. G.: Extradural hemorrhage, Brit. J. Surg. 26:346, 1938.
14. Munro, D., and Maltby, G. L.: Extradural hemorrhage: A study of 44 cases, Ann. Surg. 113:192, 1941.
15. Pringle, J. H.: Traumatic meningeal hemorrhage with a review of seventy-one cases, Edinburgh M. J. 45:741, 1938.
16. Sartorius, K., and Humphries, S. V.: Extradural hemorrhage; Twenty cases, South African M. J., 20:754, 1946.
17. Scoville, W. B.: Discussion of Turnbull.[18]
18. Turnbull, F.: Extradural cerebellar hematoma, J. Neurosurg. 1:321, 1944.
19. Vance, B. M.: Fractures of the skull. Complications and causes of death: A review of 512 necropsies and of 61 cases studied clinically, Arch. Surg. 14:1023, 1927.
20. Watts, J. W.: Discussion of Turnbull.[18]

Trophic nerves.—The question which most often presents itself for answer to the neuro-pathologist is as to the existence or non-existence of nerves directly affecting the nutrition of the tissues, apart from the changes induced in them by the section or irritation of vaso-motor nerve fibres. Without attempting to treat fully of this matter, for which, indeed, the physiological groundwork is still deficient, I shall content myself with stating the impressions in this direction which a large experience of nerve wounds has left upon my mind.

When the physiology of the vaso-motor nervous system was first elucidated by the labors of Bernard, Brown, Séquard, Schiff, and others, it was supposed that it would enable us readily to explain the many obscure phenomena which arise out of nerve wounds; but despite the able arguments of Handfield Jones and some other observers, this hope has gradually faded away, and it is now generally admitted that we must seek elsewhere for a satisfactory explanation of the facts in question.

The effects of injuries or sections of these nerves can be only to cause either contraction or dilatation of vessels, or to put a stop to the pulsatile movements which have been seen in minute vessels in many parts of the animal economy. These alterations, with the consequent changes in blood supply which they bring about, may be direct results of nerve lesions, or may be caused after partial nerve lesions by reflex influences originating in the wound. No matter how caused, they are limited to too large or too small a supply of blood, or to alterations of these conditions.

—S. Weir Mitchell in *Injuries of Nerves and Their Consequences,* published in 1872.

The Treatment of Purulent Meningitis

A. L. Sahs, M.D.

With the advent of sulfonamide and antibiotic therapy of meningitis, the former deliberate methods of managing cases of meningitis must be altered so that prompt and effective treatment can be instituted. It is gratifying to note that the mortality rate in many types of meningitis has been sharply reduced in recent years; yet many patients die, or are left with incapacitating residua because of delays in diagnosis and in the institution of adequate treatment. There are still instances of hesitancy to perform a lumbar puncture when signs of meningeal irritation are present, or when a case of unexplained fever is encountered. Delays of this type result in heightened mortality figures. In other instances, even though a lumbar puncture is performed early in the course of the disease, certain laboratory data are lacking. Thus, needless delay ensues while more cerebrospinal fluid is obtained for complete analysis. Other failures can be blamed on improper selection of chemotherapeutic or antibiotic agents, and still others are due to the development of resistance of the organism to the therapeutic drugs available at present. It is hoped that in the future more and more effective agents will be found for the control of some of the infections which do not respond to drugs now obtainable.

The widespread use of the sulfonamides and the antibiotics for infections in general has brought new problems to the physician who is interested in the subject of meningitis. Prompt administration of these drugs, although highly desirable in the treatment of an infection, may complicate the identification of the organism responsible for the meningitis. This statement should not be interpreted as a criticism of prompt utilization of the sulfonamides and antibiotics, but rather as a plea for accurate diagnosis of the type of infection at the time of the initial spinal puncture.

A partial list of microorganisms which are capable of producing purulent meningitis is shown in table 1.

GENERAL CONSIDERATIONS

The treatment of purulent meningitis consists of prompt administration of a sulfonamide and/or antibiotic preparation, employment of symptomatic and supportive meas-

From the department of neurology, College of Medicine, State University of Iowa, Iowa City, Iowa.

TABLE 1

PURULENT INFECTIONS OF THE LEPTOMENINGES

1. Bacterial (Eubacteriales)* Meningitis
   a. Neissericeae
      (1) Meningococcic (*Neisseria meningitidis*) Meningitis
      (2) Gonococcic (*Neisseria gonorrhoeae*) Meningitis
      (3) Micrococcus Catarrhalis (*Neisseria catarrhalis*) Meningitis
   b. Lactobacteriaceae
      (1) Pneumococcic (*Diplococcus pneumoniae*) Meningitis
      (2) Streptococcic (*Streptococcus pyogenes*, alpha-, and non-hemolytic streptococcus) Meningitis
   c. Micrococcaceae
      (1) Staphylococcic (*Micrococcus pyogenes* var. *aureus* and *albus*) Meningitis
      (2) Micrococcus Tetragenus (*Gaffkya tetragena*) Meningitis
   d. Parvobacteriaceae
      (1) *Hemophilus influenzae* Meningitis
      (2) *Pasturella* Meningitis
      (3) *Brucella* Meningitis
      (4) *Bacteroides* Meningitis
   e. Enterobacteriaceae
      (1) Colon Bacillus (*Escherichia coli*) Meningitis
      (2) *Aerobacter aerogenes* Meningitis
      (3) Friedlander's Bacillus (*Klebsiella pneumoniae*) Meningitis
      (4) *Proteus vulgaris* Meningitis
      (5) *Salmonella* Meningitis
   f. Achromobacteriaceae
      (1) *Alcaligenes faecalis* Meningitis
   g. Pseudomonadaceae
      (1) Pyocyaneus (*Pseudomonas aeruginosa*) Meningitis
   h. Corynebacteriaceae
      (1) Listerella (*Listeria monocytogenes*) Meningitis
      (2) Diphtheritic (*Corynebacterium diphtheriae*) and Diphtheroidal Meningitis

*After Breed, et al.[1]

ures, and isolation of the patient whenever necessary. The efficient utilization of specific therapeutic measures is dependent upon early identification of the infecting organism. In the event that the organism cannot be found or identified promptly, the physician is justified in proceeding with therapy on the basis of the clinical examination and other spinal fluid findings. Preparations which are in use at the present time are listed in tables 2, 3, 4 and 5. The present management of common forms of meningitis has been reviewed by Dowling et al.,[2] Yampolsky[3] and Nelson.[4]

The nursing and general care of these patients is essentially the same as in other acute infectious diseases. Confinement to bed in a warm, quiet, well ventilated room is advisable. If photophobia is troublesome, the room should be darkened. Constant attendance of a nurse is advisable during the acute stages, and it may be necessary at times to apply bed restraints to the delirious patient. If restlessness is conspicuous, if insomnia predominates or if convulsions occur, a sedative such as phenobarbital or one of the equivalent barbiturates should be administered. Paraldehyde, chloral hydrate or sodium bromide can also be used for sedation, but morphine or similar hypnotic drugs should be avoided. Analgesics such as acetylsalicylic acid should be given

for headache; an ice bag may also give some relief. When excitement is present or when delirium tends to exhaust the patient, cool packs can be utilized should sedatives fail to control the increased activity. Tepid baths or alcohol sponges should be used to lower an excessively high temperature. Intranasal oxygen is a useful supportive measure in severe infections. A liquid diet should be offered to the patient as soon as he is able to take nourishment. Careful attention should be paid to oral hygiene, elimination and the prevention of bedsores or abrasions resulting from protracted bed rest or restlessness. Daily computations of the liquid intake, the amount of fluid vomited and the urinary output are essential to proper management. These items are of particular significance when the sulfonamide compounds are used. The average adult should receive and retain 3,000 to 3,500 ml. of fluid daily. If that amount cannot be taken by mouth, parenteral administration of fluid is essential. Similarly, the urinary output should average 1,200 to 1,500 ml. daily; a sudden sharp decline in the volume of urine may mean retention of urine in the bladder or one of the renal complications of sulfonamide therapy.

The total amount of fluid needed by a baby in 24 hours is approximately 150 ml. per kilogram of weight (2.5 ounces for each pound). The basic chloride requirement for 24 hours is supplied by 100 to 150 ml. of saline solution (approximately 1 gm. of sodium chloride). More should not be given except in case of chloride deficiency, as produced by alkalosis from vomiting or continued loss of chloride through diarrhea. In severe diarrhea the amount of chloride given should be one and one-half to twice the basic requirement. The remaining fluid requirement should be supplied by fluids that do not contain chloride; these can be glucose, lactate or amino acid solution as indicated, when all fluids are being given parenterally. When babies are maintained completely by parenteral alimentation, the basic energy and protein requirement may be considered as 50 calories and 2 gm., respectively, per kilogram of body weight each 24 hours.

When alkaline solutions are needed to correct acidosis, it is best to give only an amount sufficient to increase the plasma CO_2 no higher than 40 volumes per cent. As a dehydrated baby rehydrates, base may become available from the tissues in sufficient amount to produce alkalosis if the plasma CO_2 has been restored fully to normal.

When babies are receiving partial or total parenteral therapy, a special chart for recording amounts of the various fluids is a convenience. The chart should be devised to show the total intakes of fluid, calories, protein, potassium chloride and sodium chloride. It should contain a column for each of the following: food and fluids given orally; bicarbonate and lactate solutions; dextrose in water; dextrose in salt solution; salt solution; Darrow's solution; plasma and blood; amino acid-dextrose solution. The caloric value for each milliliter of solution is as follows: 5 per cent dextrose, 0.2; 10 per cent dextrose, 0.4; 5 per cent amino acid solution, 0.2.

Blood transfusions are indicated as supportive measures, or when severe anemia develops as a result of the infection or the administration of sulfonamide drugs.

Another situation which must be carefully appraised presents itself when purulent meningitis occurs secondary to a suppurative lesion adja-

cent to the meninges, and concerns surgical management of the primary focus. This focus should be drained as soon as the sulfonamide or antibiotic concentration in the blood has reached a satisfactory level. With present methods of therapy it is usually unnecessary to delay surgical measures more than a few hours.

The period of convalescence is determined by the clinical course of the disease. During the period of convalescence the patient should be kept under close observation so that a relapse may be detected and specific therapy resumed promptly. The average isolation period for cases of meningococcic meningitis is two weeks.

SULFONAMIDE THERAPY

There are numerous sulfonamide preparations available to the physician today. Sulfadiazine is the preparation of choice, although sulfamerazine, sulfathiazole and sulfaguanidine are sometimes used. More recently Gantrisin has been utilized.[5] Administration of any of the sulfonamide derivatives involves certain therapeutic principles common to all. The ultimate aim is to establish and maintain an effective concentration of the drug in the blood and cerebrospinal fluid. Dosage, which is adjusted to the weight of the patient, is essentially the same for all sulfonamide drugs (table 2). Satisfactory blood levels usually range from 10 to 15 mg. per 100 ml. If blood is to be drawn for determination of sulfonamide levels, the optimum time is approximately two hours prior to the next dose of the drug. The concentration of the drug in the cerebrospinal fluid is never as high as in the blood; the ratio between the two varies with different compounds. Because it is important to attain effective levels promptly, it is desirable to give a relatively large initial dose of a sulfonamide compound. In the acute stages of meningitis the initial dose should be given parenterally in physiologic salt solution or dextrose. After the initial dose, the level is maintained by administering equal fractions of the total 24 hour dose at regular four hour intervals day and night by the oral route. The parenteral route should be continued in all cases in which the drug cannot be taken or retained by mouth. It is desirable to administer the sulfonamide compounds in full dosage throughout the acute stage of meningitis and to continue until the temperature has remained normal for four or five days, then gradually reduce the dosage before discontinuing therapy. Frequent, preferably daily, estimations of the concentration of the sulfonamide preparation in the blood will be the best guide as to the adequacy of dosage. They will also provide a safeguard against renal complications, which are often manifested by a sudden dramatic rise in the blood sulfonamide level.

The use of alkali in combination with the sulfonamide drugs is recommended to increase the solubility of the sulfonamide compounds in the urine. When the urinary output is adequate, and when the reaction of the urine is neutral or alkaline, the risk of renal complications from the sulfonamide drugs is reduced. Sodium bicarbonate should be given in divided doses totaling 12 to 15 gm. for the adult over a 24 hour period. Another method of rendering the urine alkaline is by administration of 1,000 to 2,000 ml. of a sterile solution of 1/6 molar sodium-r-lactate solution daily by the intravenous route. The sodium salts of the sulfonamide drugs should not be dissolved in this lactate solution. Alkaline solutions must be given

TABLE 2

SULFONAMIDE THERAPY OF MENINGITIS (SULFADIAZINE)*

Route	*Dosage*		
	Adult	*Child (Above 2 Years)*	*Infant*
Oral	*Initial:* 4 gm.	1.5 to 3 gm.	0.08 to 0.1 gm. per kg.
	*Maintenance:*** 1 gm. every 4 hours.	0.33 to 0.66 gm. every 4 hours.	0.033 gm. per kg. every 4 hours.
Parenteral (Sodium Sulfadiazine)	*Initial:* 5 gm. in 1000 ml. physiologic saline solution, intravenously.	1.5 to 3 gm. in 500 ml. physiologic saline solution, intravenously.	0.1 gm. per kg., intravenously in 100 to 300 ml. physiologic saline.
	*Maintenance:*** 2 to 4 gm. every 12 hours, in 1000 ml. physiologic saline solution, intravenously.	1.0 to 2 gm. in 500 ml. physiologic saline solution intravenously every 12 hours.	0.05 gm. per kg. every 6 to 12 hours in physiologic saline.

*Minor variations for other sulfonamide preparations.
**Blood level of 10-15 mg. of sulfonamide per 100 ml. should be maintained.

with considerably more caution to infants and small children.

The urine should be examined daily for the presence of blood. Microscopic hematuria is quite common; if not too many red blood cells appear in the urine, one may safely continue the drug. Gross hematuria, on the other hand, calls for discontinuance of sulfonamide medication. Occasionally lower abdominal pain precedes the appearance of gross hematuria.

Certain toxic reactions may follow the administration of sulfonamide drugs. Sulfadiazine produces fewer reactions than some of the other preparations, and hence is the drug most frequently used. These reactions, which include nausea and vomiting, drug fever, renal complications, dermatitis, hematologic complications, stomatitis, ocular and auditory disturbances, joint manifestations and peripheral neuritis, will not be discussed in detail. The adverse reactions to the sulfonamides have been reviewed by Eilert.[6]

PENICILLIN THERAPY

Penicillin is one of the safest and most effective antibiotics available today. It is useful for infections due to most gram-positive cocci and a few gram-negative cocci. There is considerable variation in the dosage schedule for penicillin; the amounts may vary from several hundred thousand to several million units per day. Table 3 gives the approximate dosage schedule.

Local reactions occur at the site of injection of penicillin and occasionally abscess formation results. Fortunately, the general and distant effects are rather few. The most troublesome manifestation of this type appears to be that of allergic sensitization. This may manifest itself as uticaria, the Arthus phenomenon and related disturbances, largely restricted to the skin and mucous membranes. Occasionally penicillin produces exfoliative dermatitis.

There is no doubt that penicillin is an irritant when it is introduced into the subarachnoid space.[7, 8] The size

TABLE 3

DOSAGE OF PENICILLIN IN TREATMENT OF MENINGITIS

Route	*Dosage*		
	Adult	*Child (Above 15-20 kg.)*	*Infant*
Parenteral	50,000 to 100,000 units* intramuscularly in physiologic saline solution every 3 hours,	Same as adult	1,500 units* per kg. intramuscularly in physiologic saline every 3 hours,
	or		or
	Procaine penicillin 300,000 units once or twice daily,	Same as adult	Procaine penicillin (suspended in water) 3,000 units per kg., one daily injection,
	or		or
	Intravenous penicillin* 1-3 million units in physiologic saline solution daily	Same as adult	Intravenous penicillin,* 500,000 to 1,000,000 units daily
Intrathecal	20,000 units* daily. This amount should be dissolved in 10 ml. of physiologic saline solution before injection.	Same as adult	5,000 to 10,000 units* daily. This amount should be dissolved in 5 ml. of physiologic saline before injection.

*Aqueous penicillin, sodium or potassium form

of the individual dose, the concentration of the solution injected, the frequency of injection, and the duration of intraspinal therapy, are factors of importance in consideration of this problem. A pleocytosis may follow a single intrathecal injection.[9] More alarming reactions, in the form of convulsions, myelitis, arachnoiditis and others have been reported.[10, 11, 12] A great deal of controversy still exists regarding the necessity of using intrathecal therapy. Most authors report preference for this route in severe infections.

STREPTOMYCIN THERAPY

Streptomycin is being replaced in the treatment of many infections by the newer antibiotics such as Aureomycin and chloramphenicol. Long[13] has recently shown how Aureomycin and chloramphenicol have replaced streptomycin in the treatment of a variety of infections. Streptomycin still occupies first place in the treatment of tuberculosis, plague, and in proteus and some pyocyaneus infections.

Local irritation may occur at the site of injection of streptomycin solutions. Streptomycin is also irritating when it is introduced into the subarachnoid space.[14] Meningeal signs, root pains, paresthesias and temporary partial paraplegia occur, particularly when the larger doses are employed intrathecally. Precautions regarding dilution should be observed when streptomycin is introduced in the subarachnoid space.

The general and distant effects resulting from the administration of streptomycin will not be discussed in detail. Circumoral paresthesia, nausea, vomiting, stomatitis, fever, jaundice, psychosis, blood dyscrasias, sensitivity reactions, skin eruptions and renal damage are some of the abnormal reactions which have been encoun-

TABLE 4

STREPTOMYCIN THERAPY OF MENINGITIS

Route	*Dosage*	
	Adults	*Children*
Parenteral	0.5 to 1.0 gm. every 8 hours intramuscularly.	0.015 gm. per kg. every 8 hours intramuscularly.
Intrathecal	0.05 gm. daily. This amount should be dissolved in 10 ml. physiologic saline solution.	0.025 gm. daily. This amount should be dissolved in 5 ml. physiologic saline solution.

tered.[15] Complications referable to the eighth cranial nerves, producing vertigo and deafness, are to be feared if streptomycin therapy has to be continued three weeks or more. Dihydrostreptomycin has, in many instances, replaced the original form, but may be somewhat inferior to streptomycin in point of therapeutic efficiency. Evidence is accumulating that dihydrostreptomycin is also neurotoxic. The usual symptoms of intoxication are vertigo, aural noises, headache, nausea and vomiting, followed by disturbances of gait and posture and blurring of distant visual objects. Nystagmus is rarely seen. Loss of vestibular reactions to rotatory and caloric tests takes place if the medication is continued, and hearing becomes progressively impaired. Once lost, hearing is not restored. Thus the decision to continue streptomycin therapy must depend upon the seriousness of the infection, the resistance of the organism and the inability to substitute one of the other antibiotics. The dosages of streptomycin are listed in table 4.

AUREOMYCIN THERAPY

This drug is readily absorbed when given by mouth, and adequate concentrations may persist for six to eight hours after a single dose of 300 to 700 mg. in an adult. Whitlock et al.[16] have demonstrated satisfactory blood levels of Aureomycin four and six hours after a single oral dose of 11 mg. per kg. in children. Intramuscular administration of this drug is not recommended because of the irritating effects by this route, but it can be given intravenously to those people who are unable to take medication by mouth. Because of the possibility of thrombophlebitis at the site of injection, intravenous therapy should be discontinued as soon as the patient can take Aureomycin orally. Nausea, vomiting and diarrhea sometimes occur during the administration of this drug. Glossitis, stomatitis and skin eruptions have been reported.[17] The dosages of Aureomycin are shown in table 5.

Aureomycin is effective in a variety of infections due to staphylococcus aureus, streptococcic and pneumococcic organisms and *H. influenzae*. It is useful in the treatment of infections due to gram-negative bacilli, such as those of the coli-aerogenes group. Aureomycin has been used in the treatment of infectious mononucleosis and lymphogranuloma venereum.

CHLORAMPHENICOL THERAPY

Chloramphenicol is effective against many species of gram-positive cocci and gram-negative organisms, both cocci and bacilli. It is also effective against Rickettsiae. Brucella infections respond to this drug. It is per-

TABLE 5

DOSAGE OF ANTIBIOTICS OTHER THAN PENICILLIN AND STREPTOMYCIN

	Adult	*Child*
Aureomycin	Oral: 500 mg. every 6 hours.	Oral: 15 mg. per kg. every 6 hours.
	Intravenous: 500 mg. every 12 hours.	Intravenous: 7 mg. per kg. every 12 hours.
Chloramphenicol	Oral: 750 mg. every 6 hours.	Oral: 750 mg. initially; 250 mg. every 4 hours.
Bacitracin	Intramuscular: 10,000 to 25,000 units every 4 hours.	Intramuscular: 400 units per kg. every 6 hours.
	Intrathecal or intraventricular: 5,000 units daily.	Intrathecal or intraventricular: 500 units daily.
Terramycin	Oral: 0.5 gm. every 4 hours.	Oral: 10 mg. per kg. every 4 hours.
	Intravenous: 0.5 gm. every 12 hours.	Intravenous: 0.25 to 0.5 gm. every 12 hours.
Polymyxin	Oral: 100 mg. every 4 hours.	Oral: 2 mg. per kg. every 4 hours.

haps the most effective antibiotic against typhoid fever and some of the other Salmonellae. Influenzal meningitis has been successfully treated with chloramphenicol by Prather and Smith.[18] The dosages are listed in table 5. The drug is administered by mouth.

Toxic reactions occur in the course of therapy with this antibiotic.[17] Nausea, vomiting and mild skin eruptions have been noted. Frequent loose stools may occur. Severe neutropenia has been reported.[19]

BACITRACIN THERAPY

Bacitracin has a spectrum similar to that of penicillin, but it is effective against many strains of gram-positive cocci which are resistant to penicillin. The superiority of Bacitracin is offset by the development of the lower nephron syndrome following parenteral administration of the drug in about 16 per cent of cases. Teng and Meleney,[20] Teng,[21] and Teng, Cohen and Meleney[22] reported on the use of Bacitracin by the intramuscular, subarachnoid and intraventricular routes, particularly in penicillin-resistant staphylococcic meningitis. They indicated that large and repeated doses of Bacitracin can be administered directly to the central nervous system without causing toxic or irritative signs. Synergism between Bacitracin and penicillin should be tested, and if present, would indicate the use of both drugs. The dosages are listed in table 5.

TERRAMYCIN THERAPY

This antibiotic is effective against a variety of organisms, with a range similar to that of Aureomycin. Thus it can be used against gram-positive and gram-negative bacteria, the rickettsiae and certain of the viruses,[23, 24] but the exact place of this drug in the treatment of meningitis has not been established. There is a low incidence of side reactions. In occasional instances, severe gastrointestinal distress, including diarrhea, may necessitate withdrawal of the drug.[25] The dosages are shown in table 5.

POLYMYXIN THERAPY

Polymyxin (Aerosporin) is not a pure substance. It is highly specific against gram-negative bacterial infec-

tions; thus far it is the most powerful agent against some strains of *Pseudomonas aeruginosa*.[26, 27] Polymyxin has been reported effective in *Hemophilus influenzae meningitis* after streptomycin, sulfadiazine and specific rabbit anti-influenzal serum had not produced a cure.[28] One of the principal disadvantages in its use is the fact that the drug is nephrotoxic. The dosages are listed in table 5.

NEOMYCIN THERAPY

In view of the ototoxic and nephrotoxic effects of Neomycin, this drug cannot be recommended for general use at this time.[29]

MENINGOCOCCIC MENINGITIS

The usual isolation period is two weeks. In the treatment of meningococcic meningitis, most clinicians prefer sulfadiazine to penicillin, although these drugs are often used in combination. Other preparations, such as sulfamerazine or Gantrisin,[5] have been used occasionally. Satisfactory results have been reported from the use of chloramphenicol.[30] It is usually advisable to administer the initial dose of sodium sulfadiazine by the intravenous route and to give a second intravenous injection in six to 12 hours. A blood level of 10 to 15 mg. per 100 ml. is preferable. Thereafter, the drug is given orally if possible. The average length of treatment is between eight and nine days. Sometimes the patient will be well on the road to recovery in five days' time.

An increasing number of physicians are discarding intrathecal injections in meningococcic meningitis.[31] The intrathecal route is sometimes utilized as a desperation procedure, nevertheless. The general measures are reviewed earlier in this paper.

Careful attention must be paid to the possibilities of fulminating meningococcic septicemia and massive bilateral adrenal hemorrhages. The use of additional measures, such as adrenal cortical extract, would be indicated under these circumstances.[32] The causes of death in meningococcic infection are reviewed by Daniels.[33]

GONOCOCCIC MENINGITIS

Gonococcic meningitis is an uncommon type caused by *Neisseria gonorrhoeae*. This type of infection occurs more commonly in young male adults, and, as a rule, is secondary to a genital infection.[34] At times meningitis is the only complication, but other lesions such as arthritis, endocarditis or a purpuric cutaneous rash also may be present. The blood culture may be positive. The mortality rate prior to the introduction of sulfonamides and antibiotics was 45 per cent.[35] With the present day use of these preparations, the mortality rate should decline sharply. The specific treatment and general supportive measures are the same as those discussed under meningococcic meningitis.

MENINGITIS CAUSED BY MICROCOCCUS CATARRHALIS

Meningitis caused by the micrococcus catarrhalis (*Neisseria catarrhalis*) occurs with extreme rarity. As a rule it possesses low virulence, and is encountered in conjunction with respiratory tract infections.[36] Meningitis caused by *Neisseria catarrhalis* occurs during childhood, but has been reported in adults. It has terminated fatally in the majority of cases. It would seem advisable to use sulfadiazine by the usual routes and to supplement with the antibiotic preparation to which the organism was most sensitive. Possibly Terramycin will prove to be an effective antibiotic.

OTHER NEISSERIAN INFECTIONS OF THE LEPTOMENINGES

Occasional reports are found in the

literature implicating other members of the Neisseria group. Bansmer and Brem[37] reported a case of meningitis due to *Neisseria sicca*, with a satisfactory response to intravenous sulfadiazine, intramuscular streptomycin, intrathecal penicillin and oral glucosulfadiazine. Meningitis due to *Neisseria sicca* has usually been reported during the course of an endocarditis due to this organism.[38]

Neisseria perflava was the invading organism in the case reviewed by Sophian.[39] Atypical Neisseria are occasionally implicated.

PNEUMOCOCCIC MENINGITIS

Prior to the advent of chemotherapy, the mortality rate from pneumococcic meningitis approximated 100 per cent. Use of the sulfonamides has decreased this figure, and the combined use of a sulfonamide preparation and penicillin now has reduced the mortality still further. However, the problem of the treatment of pneumococcic meningitis has not yet been satisfactorily solved; this situation may be due to the fact that a primary focus of infection may be most difficult to find. Relapses are likely to occur, although an initial favorable response will be noted in the majority of cases. The present mortality figures range from 30 to 50 per cent. The report of Appelbaum et al.,[40] with 73 per cent recoveries, is distinctly encouraging.

As soon as the diagnosis is made or strongly suspected, penicillin should be administered by the intramuscular and intrathecal routes. It is essential that penicillin therapy be continued in daily injections until the spinal fluid has been sterile for five or six days. Penicillin resistance seldom proceeds rapidly.[41] Dowling et al.[42] utilized massive intramuscular doses in the treatment of pneumococcic meningitis. In addition to penicillin, sulfonamides should be administered in relatively large doses, so that a concentration of 15 to 18 mg. per 100 ml. is reached in the blood as rapidly as possible. Sulfadiazine is the drug of choice. Sulfonamide therapy is maintained for approximately 10 days after the temperature has returned to normal. Type specific antiserum is no longer utilized. The usual supportive measures are indicated.

Careful search should be made for a possible source of infection in these cases, particularly in the sinuses, middle ears and mastoids. A possible brain abscess, or a previously unrecognized compound skull fracture, should always be kept in mind as the possible source of a continuing infection. If such a focus is found, it should be managed according to accepted surgical principles.

The importance of early diagnosis and prompt institution of vigorous therapy must again be emphasized. Delays in either instance will result in increased mortality figures and complications. Relapses and reinfections must be guarded against.

STREPTOCOCCIC MENINGITIS

The treatment of the beta-hemolytic group of streptococcic infections involves the use of an antibiotic and a sulfonamide preparation. Penicillin is the antibiotic of choice, with streptomycin, Aureomycin and Terramycin as other possibilities, depending upon sensitivity studies. Sulfadiazine is indicated in the usual dosage. So far as the alpha-hemolytic (viridans) group is concerned, about 10 per cent of the strains are resistant to penicillin.[43] Successful treatment may depend on the use of sensitivity tests against the offending organism. When the organism is obtained from the spinal fluid, its sensitivity to each

of the sulfonamides, to penicillin and to streptomycin should be determined. The drugs found to be most powerful against the specific strain should be selected, and with such dosage as to secure blood levels (and consequently spinal fluid levels) well above the minimal sensitivity concentration. Thus sulfadiazine and either penicillin or streptomycin may prove to be the most effective combination. Blood transfusions may be indicated for severe anemia.

Non-hemolytic streptococcic meningitis is most often an accompaniment of subacute bacterial endocarditis. Penicillin and streptomycin are the antibiotics of choice, but the problem of drug resistance is a very significant one. Aureomycin may be useful in certain instances.[44]

STAPHYLOCOCCIC MENINGITIS

Staphylococcic meningitis is usually caused by *Micrococcus pyogenes* var. *aureus*, but in 20 to 25 per cent of all cases the causative organism is var. *albus*. Generally, infection of the meninges is secondary to a staphylococcic infection elsewhere in the body, although the original lesion may be quiescent before meningitis develops.

The treatment of staphylococcic meningitis of either type centers primarily on the use of penicillin and sulfadiazine in the usual doses and by the usual routes. Intrathecal penicillin is ordinarily included in the treatment. Therapy should be continued for several weeks after the infection has apparently subsided, and the patient should be kept under observation for an even longer period of time, because of the possibility of relapse. A local suppurative focus should be treated by surgical drainage whenever found.

Since penicillin has come into use, it appears that some strains of staphylococcus are resistant to this preparation.[45] There is some evidence that the number of penicillin-resistant strains of this organism is increasing. During the original diagnostic procedures and throughout the course of therapy, it should be remembered that sensitivity and resistance studies are of great importance. It may be necessary to alter the medication, and to employ streptomycin, Aureomycin, Terramycin, chloramphenicol and Bacitracin[20] in various combinations.

Recovery from meningitis due to the staphylococcus was reported only rarely prior to the advent of the sulfonamides; the disease had a mortality rate approaching 100 per cent. Modern therapy has resulted in a significant drop in the mortality from this disease.

MENINGITIS CAUSED BY MICROCOCCUS TETRAGENUS

A rare invader of the nervous system, *Gaffkya tetragena*, is sometimes responsible for meningitis. Although it is commonly present in the upper respiratory tract, the organism becomes invasive under unusual circumstances, such as states of lowered resistance. Penicillin is the antibiotic of choice. The value of the sulfonamide compounds in the treatment of this type of infection is questionable, although Criscitiello's[46] case recovered after sulfanilamide therapy. A review of the subject by Leach and Medinger[47] revealed five recoveries among eight patients. Three of the recoveries took place in the era before the use of sulfonamides.

HEMOPHILUS INFLUENZAE MENINGITIS

The treatment of influenzal meningitis underwent a profound transition with the introduction of chloramphenicol. Previously the therapy centered around streptomycin, sulfonamide and serum. The gratifying re-

ports of Prather and Smith[18] and of McCrum et al.,[48] noting the rapid disappearance of organisms from the spinal fluid after the institution of chloramphenicol therapy, may make other modes of treatment obsolete. In the age group from one to five years, the initial oral dose is approximately 750 mg. Subsequent doses of 250 mg. every four hours will maintain an adequate blood and spinal fluid concentration. Rectal administration of 500 mg. will enhance the orally administered drug.

Certain cases may still require supplemental therapy, however, through the use of some of the preparations which have proven quite effective in the past.[49] Intramuscular streptomycin and penicillin have been utilized. Many clinicians have used streptomycin intrathecally. Hoyne and Brown[50] have taken exception to this route by indicating that intrathecal therapy is not necessary in the management of *H. influenzae* meningitis. It has been the policy in the past to maintain a sulfonamide blood level of 10 to 15 mg. per 100 ml., in addition. Supplemental therapy with type b specific rabbit serum intravenously has also been utilized.

The mortality rate in influenzal meningitis was 95 per cent or greater before the introduction of specific measures. With combined therapy the mortality figures have dropped to the neighborhood of 20 per cent. Chloramphenicol will undoubtedly reduce these figures to a lower level.

MENINGITIS DUE TO OTHER PARVOBACTERIACEAE

Pasturella pestis is sometimes responsible for meningitis.[51] Tularemic meningitis is a rare complication of infection with *Pasturella tularensis*.[52] Occasionally other members of the *Pasturella* group are responsible for infections of the meninges.[53] The combination of a sulfonamide preparation with streptomycin or Aureomycin is indicated for the treatment of infections of this type.

Brucellosis meningitis is occasionally reported as a subacute infection.[54] Any of the three varieties, *Brucella melitensis*, *Brucella abortus* or *Brucella suis*, may be responsible. Chloramphenicol, Aureomycin and streptomycin have been used alone and in combination. The illness is usually protracted, and therapy must be carried out for long periods of time.

Meningitis due to *Bacteroides* is an infrequent accompaniment of septicemia or chronic suppurative otitis media.[55, 56] The diagnosis rests on the cultivation of the organism by anaerobic methods. The mortality in the past has been 100 per cent. More recently, sulfonamides have been effective in some cases. At the present time Aureomycin is the antibiotic of choice.

MENINGITIS DUE TO THE COLI-AEROGENES AND SALMONELLA GROUPS

The treatment of meningitis due to *Escherichia coli* has gradually evolved to the use of streptomycin by the intramuscular and possibly the intrathecal routes.[57, 58] The introduction of Aureomycin and chloramphenicol may alter the picture, but in the light of our present knowledge, there would seem to be justification in starting treatment with streptomycin and changing to one of the other antibiotics if the sensitivity studies indicated greater sensitivity to Aureomycin or chloramphenicol.

Aerobacter aerogenes is a very infrequent invader of the nervous system. Infections due to this organism should be treated with streptomycin[59] or one of the other antibiotics such as Aureomycin[60] or chloramphenicol.

Klebsiella pneumoniae meningitis is

also of rather uncommon occurrence. Most infections of this type have terminated fatally in the past.[61] The treatment of choice is streptomycin[62] by the intramuscular and possibly the intrathecal route. Either Aureomycin or chloramphenicol can be used as alternate antibiotics.

Proteus vulgaris is occasionally capable of producing meningitis.[63] The most useful antibiotic in the treatment of an infection due to this organism is streptomycin,[64] which can be utilized by the intramuscular and possibly the intrathecal route. The usual supportive and surgical measures are in order. Chloramphenicol may be a useful adjunct.

The genus *Salmonella* is composed of many different species and types. Apparently any organism of this group might be expected to cause meningitis.[65] *S. typhosa, S. enteritidis, S. paratyphi B.* and *S. havana* have been most frequently reported as etiologic agents. The sulfonamides apparently resulted in a reduction of the over-all mortality rate. Later, the combination of streptomycin and a sulfonamide preparation were used, with increased effectiveness. At the present time chloramphenicol is the preferred antibiotic, particularly in typhoid fever. Aureomycin may also prove of value in certain cases.[66]

ALCALIGENES FAECALIS MENINGITIS

Alcaligenes faecalis is generally considered to be non-pathogenic for man.[67] *A. faecalis* has been associated with a variety of clinical conditions such as polyarthritis and hepatitis.

The clinical manifestations do not differ appreciably from those of other types of acute bacterial meningitis. Streptomycin by the intramuscular route, and occasionally intrathecally, seems to be the antibiotic of choice. Sulfadiazine may be used in addition.

PYOCYANEUS MENINGITIS

Pyocyaneus meningitis is another comparatively rare type, but is assuming increased importance because of the frequency with which spinal punctures are being performed. The causative organism, *Pseudomonas aeruginosa*, is encountered most commonly as a saprophyte on the skin or in the upper respiratory tract. The treatment of *Pseudomonas aeruginosa* infection of the subarachnoid space depends in part on sensitivity studies. Streptomycin by the intramuscular and intrathecal routes, plus sulfadiazine, has been used successfully.[68, 69] More recently, Aureomycin has been reported as effective in a streptomycin-resistant case.[60] Treatment is usually protracted, and the possibility of relapse following discontinuance of drug therapy is to be guarded against.

The previous mortality rate of approximately 80 per cent has now been lowered to 50 per cent or below. It is evident that this infection is still a serious and troublesome one. Strict asepsis is necessary whenever a needle is placed in the subarachnoid space, either for a diagnostic lumbar puncture or for the instillation of a spinal anesthetic or other material. There is ample evidence to show that pyocyaneus meningitis has appeared during intrathecal therapy for meningitis of another type.[70]

LISTERELLA MENINGITIS

Meningitis caused by *Listeria monocytogenes* has been occasionally encountered.[71] In human cases, both the source of the infection and the portal of entry have been obscure. The evidence suggests, however, that a septicemia precedes the meningeal invasion. This organism must be differentiated bacteriologically from *Erysipelothrix rhusiopathiae*. Experimen-

tal data, coupled with the favorable results of treatment of this infection in animals, point to the use of either chloramphenicol or Aureomycin in this disease.

DIPHTHERITIC AND DIPTHEROIDAL MENINGITIS

Medical literature contains only a few references to meningitis caused by *Corynebacterium diphtheriae*[72] or to the diphtheroid bacilli.[73] When meningitis is caused by *C. diphtheriae*, specific antiserum should be administered. The intravenous route should be utilized in severely ill patients. Penicillin by the usual routes should be used as adjunctive therapy. There are no special therapeutic measures for meningitis caused by the diphtheroid bacilli.

SUMMARY AND CONCLUSIONS

The prompt diagnosis of meningitis and the rapid identification of the infecting organism is of utmost importance in the present day management of this type of infection of the nervous system. Sensitivity and resistance studies will give the clinician accurate data on which to plan his therapeutic program. The sulfonamides and the antibiotics, alone or in combination, have greatly reduced the mortality rates in a number of types of purulent meningitis; yet many patients die or are left with incapacitating residua because of delays in diagnosis and in the institution of adequate treatment. In his enthusiasm to apply the principles of modern chemotherapy and antibiotic therapy, the physician should not forget the importance of general care of the patient with purulent meningitis. Furthermore, he must be constantly on the alert to detect and to drain any focus of infection which might be responsible for contaminating the subarachnoid space.

REFERENCES

1. Breed, R. S.; Murray, E. G. D., and Hitchens, A. P.: Bergey's Manual of Determinative Bacteriology, ed. 6, Baltimore, Williams and Wilkins Company, 1948.
2. Dowling, H. F.; Sweet, L. K.; Hirsh, H. L., and Lepper, M. H.: Specific therapy of bacterial infections of central nervous system, J. A. M. A. 139:755, 1949.
3. Yampolsky, J.: Treatment of common forms of meningitis, M. Clin. North America 33:871, 1949.
4. Nelson, W. E.: Meningitis and encephalitis in infants and children, M. Clin. North America 34:1679, 1950.
5. Rhoads, P. S.; Svec, F. A., and Rohr, J. H.: Bacterial meningitis: results of treatment in 17 cases with new sulfonamide (Gantrisin), Arch. Int. Med. 85:259, 1950.
6. Eilert, M. L.: Adverse reactions to the sulfonamides and antibiotics, M. Clin. North America 31:31, 1947.
7. Erickson, T. C.; Masten, M. G.; and Suckle, H. M.: Complications of intrathecal use of penicillin, J. A. M. A. 132:561, 1946.
8. Walker, A. E.: Toxic effects of intrathecal administration of penicillin, Arch. Neurol. & Psychiat. 58:39, 1947.
9. Rammelkamp, C. H., and Keefer, C. S.: The absorption, excretion and toxicity of penicillin administered by intrathecal injection, Am. J. M. Sc. 205:342, 1943.
10. Johnson, H. C.; Walker, A. E.; Case, T. J., and Kollros, J. J.: Effects of antibiotic substances on the central nervous system, Arch. Neurol. & Psychiat. 56:184, 1946.
11. Millikan, C. H., and Sahs, A. L.: Adhesive arachnoiditis following intrathecal administration of penicillin, J. Iowa M. Soc. 37:198, 1947.
12. Reuling, J. R., and Cramer, C.: Intrathecal penicillin, J. A. M. A. 134:16, 1947.
13. Long, P. H.: The clinical use of antibiotics, M. Clin. North America 34:307, 1950.
14. Pilcher, C., and Smith, E. R.: The effects of intramuscular and intrathecal administration of streptomycin in normal dogs and in dogs with meningitis due to Escherichia Coli, Ann. Surg. 129: 810, 1949.

15. Farrington, R. F.; Hull-Smith, H.; Bunn, P. A., and McDermott, W.: Streptomycin toxicity; reactions to highly purified drug on long-continued administration to human subjects, J. A. M. A. 134:679, 1947.
16. Whitlock, C. M., Jr.; Hunt, A. D., Jr., and Tashman, S. G.: Aureomycin dosage schedules for children, Pediatrics 6:827, 1950.
17. Harris, H. J.: Aureomycin and chloramphenicol in brucellosis, with special reference to side effects, J. A. M. A. 142:161, 1950.
18. Prather, G. W., and Smith, M. H. D.: Chloramphenicol in the treatment of Hemophilus Influenzae meningitis, J. A. M. A. 143:1405, 1950.
19. Volini, I. F.; Greenspan, I.; Ehrlich, L.; Gonner, J. A.; Felsenfeld, O., and Schwartz, S. O.: Hemopoietic changes occurring during administration of chloramphenicol (chloromycetin), J. A. M. A. 142:1333, 1950.
20. Teng, P., and Meleney, F. L.: The treatment of staphylococcic meningitis; with a review of the literature and with particular reference to the results with bacitracin; a report of five cases, Surgery 28:516, 1950.
21. Teng, P.: Further experiences in treatment of septic meningitis with bacitracin, Arch. Neurol. & Psychiat. 64: 861, 1950.
22. Teng, P.; Cohen, I., and Meleney, F. L.: Bacitracin in neurosurgical infections, Surg. Gynec. & Obstet. 92:53, 1951.
23. Bliss, E. A.; Warth, P. T., and Chandler, C. A.: The susceptibility of gram-positive cocci, gram-negative bacilli, and clostridia to terramycin, Ann. New York Acad. Sc. 53:277, 1950.
24. Caldwell, E. R., Jr.; Spies, H. W.; Wolf, C. K.; Lepper, M. H., and Dowling, H F.: The treatment of various infections with terramycin, J. Lab. & Clin. Med. 36:747, 1950.
25. King, E. Q.; Lewis, C. N.; Welch, H.; Clark, E. A., Jr.; Johnson, J. B.; Lyons, J. B.; Scott, R. B., and Cornely, P. B.: Clinical observations on the use of terramycin hydrochloride, J. A. M. A. 143:1, 1950.
26. Hayes, E. R.: Meningitis due to Pseudomonas Aeruginosa treated with polymyxin B., Am. J. M. Sc. 220:633, 1950.
27. Tomlin, C. E.: Pseudomonas meningitis; report of a case with recovery after polymyxin B therapy, Arch. Int. Med. 87:863, 1951.
28. Kagan, B. M.: Influenzal meningitis: recovery of case of four weeks duration with use of a new drug, polymyxin B (aerosporin), Pediatrics 4:319, 1949.
29. Waisbren, B. A., and Spink, W. W.: A clinical appraisal of neomycin, Ann. Int. Med. 33:1099, 1950.
30. McCrumb, F. R.; Hall, H. E.; Meredith, A. M.; Deane, G. E.; Minor, J. V., and Woodward, T. E.: Chloramphenicol in the treatment of meningococcal meningitis, Am. J. Med. 10:696, 1951.
31. Hoyne, A. L., and Brown, R. H.: 727 meningococcic cases: an analysis, Ann. Int. Med. 28:248, 1948.
32. Bush, F. W., and Bailey, F. R.: The treatment of meningococcus infections with special reference to the Waterhouse-Friderichsen syndrome, Ann. Int. Med. 20:619, 1944.
33. Daniels, W. B.: Cause of death in meningococcic infection, Am. J. Med. 8:468, 1950.
34. Stigler, S. L., and McLester, J. S.: Gonococcic meningitis fifteen years after urethritis, J. A. M. A. 136:919, 1948.
35. Marvin, H. P., and Wilkinson, W. E.: Gonococcic meningitis, J. A. M. A. 110:800, 1938.
36. Moersch, F. P., and Thompson, L.: Meningitis due to micrococcus catarrhalis, Journal-Lancet, 48:407, 1928.
37. Bansmer, C., and Brem, J.: Acute meningitis caused by neisseria sicca, New England J. Med. 238: 596, 1948.
38. Weed, M. R.; Clapper, M., and Myers, G. B.: Endocarditis caused by micrococcus pharyngis siccus: recovery after treatment with heparin and sulfapyridine, Am. Heart J. 25: 547, 1943.
39. Sophian, L. H.: A case of acute meningitis caused by neisseria perflava, Am. J. M. Sc. 207:376, 1944.
40. Appelbaum, E.; Nelson, J., and Albin, M. B.: Treatment of pneumococcic meningitis with penicillin: study of 125 consecutive cases, with 73 per cent recovery, Am. J. M. Sc. 218: 260, 1949.
41. Miller, C. P.: Bacterial resistance to antibiotics, Ann. Int. Med. 29:765, 1948.
42. Dowling, H. F.; Sweet, L. K.; Robinson, J. A.; Zellers, W. W., and Hirsh, H. L.: The treatment of pneumococcic meningitis with massive doses of systemic penicillin, Am. J. M. Sc. 217:149, 1949.
43. Hoyne, A. L., and Herzon, H.: Streptococcic viridans meningitis: a review of the literature and report of nine recoveries, Ann. Int. Med. 33:879, 1950.
44. Long, P. H.; Schoenbach, E. B.; Bliss, E. A.; Bryer, M. S., and Chandler, C. A.: Experimental and clinical use of polymyxin,

chloromycetin and aureomycin, California Med. 70:157, 1949.

45. Spink, W. W., and Ferris, V.: Penicillin-resistant staphylococci: mechanisms involved in the development of resistance, J. Clin. Investigation 26:379, 1947.
46. Criscitiello, M., Jr.: Meningitis due to micrococcus tetragenus: report of a case with recovery following treatment with sulfanilamide, New England J. Med. 221: 383, 1939.
47. Leach, J. E., and Medinger, F. G.: Micrococcus tetragenus meningitis: report of a case and review of the literature, Ann. Int. Med. 15:609, 1941.
48. McCrumb, F. R., Jr.; Hall, H. E.; Imburg, J.; Meredith, A.; Hemhold, R.; Defillo, J., and Woodward, T. E.: Treatment of hemophilus influenzae meningitis with chloramphenicol and other antibiotics, J. A. M. A. 145:469, 1951.
49. Crook, W. G.; Clanton, B. R., and Hodes, H. L.: Hemophilus influenzae meningitis; observations on the treatment of 110 cases, Pediatrics 4:643, 1949.
50. Hoyne, A. L., and Brown, R. H.: Intrathecal therapy not required for H. influenzae meningitis: a report of 28 cases, J. A. M. A. 136: 597, 1948.
51. Landsborough, D., and Tunnell, N.: Observations on plague meningitis Brit. M. J. 1:4, 1947.
52. Fields, W. S.: Tularemic meningitis, Arch. Neurol. & Psychiat. 61:422, 1949.
53. Zeller, W. W., and Lepper, M. H.: Meningitis due to pasturella other than pasturella tularensis and pasturella pestis, Am. J. Med. 9:701, 1950.
54. DeJong, R. N.: Central nervous system involvement in undulant fever, with the report of a case and a survey of the literature, J. Nerv. & Ment. Dis. 83:430, 1936.
55. Beigelman, P. M., and Rantz, L. A.: Clinical significance of bacteroides, Arch. Int. Med. 84:605, 1949.
56. Smith, W. E.; McCall, R. E., and Blake, T. J.: Bacteroides infections of the central nervous system, Ann. Int. Med. 20:920, 1944.
57. Alexander, A. J.: Meningitis due to escherichia coli treated with streptomycin, J. A. M. A. 131:663, 1946.
58. Veras, S., and Mystakidis, A.: Escherichia coli meningitis treated successfully with streptomycin, Am. J. Dis. Child. 79: 115, 1950.
59. Helsper, J., and Bonzer, J.: Aerobacter aerogenes meningitis successfully treated with streptomycin, Surgery 29:131, 1951.
60. Neter, E.; Krauss, R. F.; Egan, G. J., and Mason, T. H.: Aureomycin treatment of meningitis due to bacillus pyocyaneus and bacillus aerogenes, J. A. M. A. 142:1335, 1950.
61. Ransmeier, J. C., and Major, J. W.: Friedländer's bacillus septicemia and meningitis; report of a case and autopsy, with an analysis of twenty-nine cases collected from the literature, Arch. Int. Med. 72:319, 1943.
62. Ayvazian, L. F.: Friedländer bacillus meningitis successfully treated with streptomycin, Am. J. Med. 5:470, 1948.
63. Lepow, H.; Friedenthal, M., and Jaffe, D.: Bacillus proteus meningitis, N. Y. State J. Med. 48:424, 1948.
64. Rosove, L.; West, H. E., and Bower, A. G.: Streptomycin in the treatment of proteus vulgaris meningitis, Ann. Int. Med. 32:960, 1950.
65. Henderson, L. L.: Salmonella meningitis; report of three cases and review of one hundred and forty-four cases from the literature, Am. J. Dis. Child. 75:351, 1948.
66. Ripy, H. W.: Typhoid fever in an infant complicated by typhoid meningitis; J. Pediat. 36:376, 1950.
67. Terry, L. L.; McBane, J. K., and Dean, K. F.: Bacteremia and acute meningitis due to alcaligenes faecalis, J. Lab. & Clin. Med. 32:1262, 1947.
68. Stanley, M. M.: Bacillus pyocyaneus infections; a review, report of cases and discussion of newer therapy including streptomycin, Am. J. Med. 2:253, 347, 1947.
69. Weinstein, L., and Perrin, T. S.: Meningitis due to pseudomonas pyocyanea: a report of three cases treated successfully with streptomycin and sulfadiazine, Ann. Int. Med. 29:103, 1948.
70. Harris, R. C.; Buxbaum, L., and Appelbaum, E.: Secondary bacillus pyocyaneus infection in meningitis following intrathecal penicillin therapy, J. Lab. & Clin. Med. 31: 1113, 1946.
71. Kaplan, M. M.: Listerellosis, New England J. Med. 232:755, 1945.
72. Carlson, F. G., and Morgan, H. W.: Diphtheritic meningitis; report of a case and review of the literature, J. A. M. A. 106:1164, 1936.
73. Kessel, L., and Romanoff, A.: General infection with a diphtheroid bacillus complicated by diphtheroid meningitis, J. A. M. A. 94:1647, 1930.

Neurology

Clinical Pathologic Conference

From the Division of Neurology,
Illinois Neuropsychiatric Institute

Presented by Ben W. Lichtenstein, M.D.

PRESENTATION OF CASE

A 15 year old school girl was well until July 1950 when she noted midthoracic backache and pains radiating into the chest from the site of the backache. Her family physician prescribed rest and analgesics and she progressed quite well. Weakness and awkwardness of the right lower extremity was noted in December 1950, and shortly afterwards the left lower extremity was similarly affected. In the week before her first hospital admission, she began to complain of a very severe headache associated with vomiting, and at the time of admission incontinence and diplopia were noted.

At the initial neurologic consultation she was lying in bed with her hand over one eye. She complained of severe headache, pains in the suboccipital region and inability to move the lower extremities. The mental status was good. The pupils were widely dilated but reacted well to light and on convergence, and there were no obvious signs of extra-ocular palsy. She complained of diplopia on lateral gaze in both fields, and funduscopy revealed three diopters of papilledema with very marked venous engorgement and recent hemorrhages. There was no evidence of aphasia, nor was there any facial, lingual or palatal paralysis. The corneal reflexes were present, taste was intact and there was no anesthesia in the head region.

The motor, sensory, reflex and coordination systems of the upper extremities were intact. There was a definite sensory level to pain at the fifth thoracic segment on the right and at the seventh thoracic segment on the left, with scattered areas of preserved sensation at lower levels. There was almost complete paralysis of both lower extremities, with hyperactive deep reflexes, ankle clonus and bilateral extensor plantar responses. Superficial abdominal reflexes were absent, and vibration and position sense were completely lost below the seventh thoracic segment. The temperature sense deficit corresponded more or less to the level of analgesia.

The initial impression was that of a double lesion: one to account for the papilledema and increased intracranial pressure, and another to account for the midthoracic transverse myelopathy. Although neuro-optic myelitis, or Devic's disease, produces a similar double lesion, the obvious signs of papilledema rather than papillitis and the preserved visual acuity were strong

arguments against Devic's disease. An initial lumbar puncture revealed a xanthochromic cerebrospinal fluid under 350 mm. pressure, containing 60 mg. per cent total protein. Because of the elevated pressure, a Queckenstedt's test was not performed at that time.

In attempting to diagnose the case immediately following lumbar puncture, multiple tumors of the central nervous system and its meninges were considered. At this point, it was learned that the patient's mother had recently died from polycystic disease of the kidneys and that there was a history of polycystic kidney disease in four other members of the maternal line. In view of this information, it seemed fairly certain that it was a case of Lindau's disease with an intracranial and a secondary intraspinal hemangioblastoma. It must be noted, however, that none of the cases of polycystic kidney were verified by autopsy.

The patient was transferred to another private hospital where the neurologic surgeon proposed the diagnosis of cerebellar medulloblastoma with drop metastasis to the midthoracic subarachnoid space and compression of the spinal cord. Since the increased intracranial pressure appeared to be the most urgent of the two problems, bilateral parietal burr holes were made on December 6, 1950. Ventricular estimation yielded about 50 ml. of clear, colorless cerebrospinal fluid under considerable pressure. The ventricles were not filled with air, and a surgical impression of obstructive hydrocephalus probably due to a tumor in the posterior fossa was entertained. Because of the possibility of a seeded metastatic lesion in the midthoracic region from a possible medulloblastoma or a possible leptomeningeal sarcoma of the cerebellum, a single dose of 200 roentgen units was administered at the level of the lesion. Since increased intracranial pressure persisted, an occipitocervical exploration was performed two days after ventricular estimation. A fair amount of occipital bone was removed together with the arches of the atlas and the axis. When the dura mater was opened throughout, an enlarged cisterna magna was revealed from which fluid spurted under considerable pressure. The vermis and cerebellar hemispheres appeared perfectly normal and, on separating the cerebellar tonsils, fluid could be seen passing freely out of the fourth ventricle. A catheter was passed to what must have been the cervicodorsal junction without meeting obstruction. In short, the occipitocervical exploration yielded no additional information. Since the leptomeninges covering the cistern appeared to be opaque, a biopsy for possible sarcomatosis of the leptomeninges was performed; this proved to be negative.

Although the posterior fossa exploration was negative, a diagnosis of possible Lindau's disease could still be entertained, since a hindbrain hemangioblastoma could still have been present in a non-visualized area or a hemangioblastoma could have been present above the tentorium.

A few days following occipitocervical exploration, spontaneous nystagmus was noted and intention tremor appeared in the upper extremities. The papilledema did not recede, headaches continued and deep x-ray therapy to the midthoracic region failed to relieve the paraplegia. A second lumbar puncture on December 11 revealed an initial pressure of 440 mm., with a rise to 500 mm. on jugular compression. The fluid was xanthochromic with a pink overtinge. A third lumbar puncture on December 16 revealed an initial pressure of 280 mm. of cerebrospinal fluid with a very slight rise on jugular compression. The fluid was deep yellow in color and clotted on standing.

On December 18, 1950 the patient's spinal cord was delaminated from C7 to Th3. On opening the dura, one noted a very vascular tumor mass filling the spinal subarachnoid spaces and enveloping the spinal cord. The spinal cord did not pulsate and, because of the excessive vascularity of the lesion, biopsy was not performed. On December 28, 1950 the patient was transferred to the Illinois Neuropsychiatric Institute for further study and therapy.

The course of this patient's illness from the date of laminectomy to the date of her death on March 23, 1951 was characterized by persistence of increased intracranial

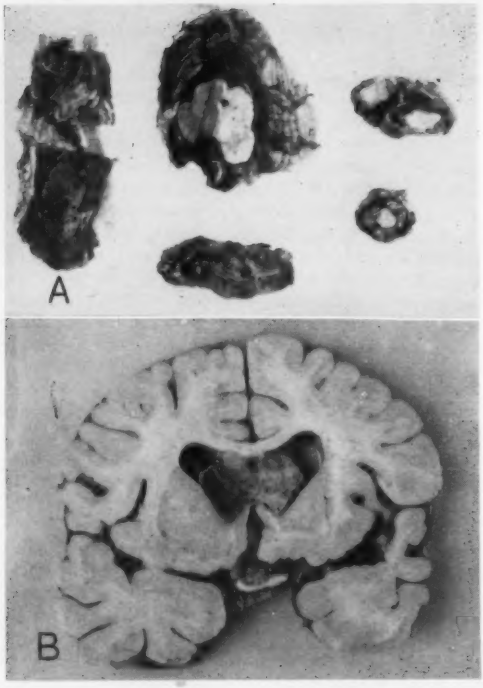


FIG. 1. A. Transverse sections through the spinal cord and the midbrain showing the deeply colored tumor in the subarachnoid spaces.

B. Coronal section of the brain showing the solid tumor masses in the lateral ventricles.

pressure, ascent of the spinal cord lesion to involve the cervical enlargement, with progressive signs of incoordination, tremor, anesthesia, reflex change and finally paralysis of the upper extremities. She became quite emaciated and lethargic, and it is significant that the involvement of the upper extremities was accompanied by such paresthesias about the shoulders and arms that neither bedclothes nor a nightgown could be tolerated. As time passed, the left lower extremity remained quite spastic while the right lower extremity became somewhat flaccid. X-ray examination of the urinary tract failed to reveal evidence of cystic disease of the kidneys. In the terminal stages, bulbar paralysis appeared.

Clinical Diagnosis: Multiple hemangioblastomas in the spinal leptomeninges and possibly in the brain or its meninges.

Final Anatomical Diagnoses: (1) Diffuse hemangio-endothelioma of multicentric origin in the leptomeninges and in the cores of the choroid plexuses of the lateral and third ventricles.

(2) Invasion of the intracerebral tumors into the juxtaventricular brain substance.

(3) Invasion of the spinal hemangio-endothelioma in the cervicothoracic region into the spinal dura mater.

(4) Extensive cervicothoracic myelopathy due to compression and interference with the circulation.

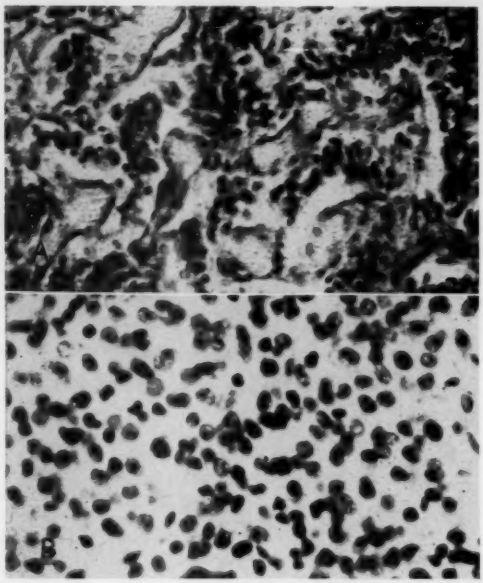


FIG. 2. A. Hemangio-endothelioma showing blood vessels and intervascular endothelial cells.

B. Higher power photomicrograph showing sheets of endothelial cells. Thionin stain.

(5) Degeneration of the spinal nerve roots compressed by the tumor.

PATHOLOGIC FINDINGS

Gross examination: With the exception of bronchopneumonia, pulmonary edema and chronic cystitis of the urinary bladder, the essential pathologic changes were limited to the central nervous system. It is significant that there were no cysts in the kidneys or in the pancreas. Gross examination of the brain revealed herniation of cerebral substance at the sites of the ventricular taps. The leptomeninges at the base of the brain and over the vermis were the seat of purplish-gray tumor masses which extended from the level of the foramen magnum to the optic chiasm. The ambient cistern was filled with tumor tissue (figure 1). Coronal sections of the brain revealed purplish-gray tumor masses in the cores of the choroid plexuses of the lateral ventricles. Similar tumor tissue was found lining the third ventricle and in the leptomeninx at the base near the temporal lobe. There was local invasion of the tumor tissue into the subependymal regions that border on the choroid plexuses.

The cervicothoracic region of the spinal cord was enveloped by a large purplish-gray tumor mass which filled the subarachnoid space. On transverse section, the cervical enlargement appeared to be softened and distorted and the dura mater in this region was thickened. Transverse sections from the level of the medulla oblongata to the cauda equina reveal a diffuse tumor mass throughout the leptomeninges.

Microscopic examination: The histological picture of the tumor was uniform throughout. The tumor was very vascular, the vessels being comprised

for the most part of precapillaries and medium-size veins. The lining of the blood vessels appeared perfectly normal. Intervascular tissue filled the spinal subarachnoid spaces enveloping the spinal cord and its nerve roots. At the base of the brain, the tumor was not as diffuse as in the spinal region. Here one saw isolated masses of tumor tissue about the basilar artery and in both cerebellopontine angles. The intervascular tumor tissue was composed of sheets of endothelial cells containing round nuclei with fine granules of chromatin scattered uniformly throughout the nucleus. There was a slight variation in the size of the nuclei but, for the most part, they were uniform. No mitotic figures were seen and no invasion of the blood vessels could be demonstrated (figure 2).

Although the spinal cord substance at the level of the cervical enlargement was virtually destroyed by compression, the pia-glial border was everywhere intact and the tumor did not invade the spinal cord substance. The pia mater spinalis was greatly thickened and served as an effective barrier. The tumor masses in the choroid plexuses of the lateral ventricles were identical in structure and, in some fields, the vascularity was unusually prominent. Here one could visualize the development of sheets of endothelial cells from budding blood vessels. The ependymal lining of the third ventricle was destroyed and replaced by the tumor mass which invaded the cerebral substance at variable depths. At these sites, the sheets of endothelial cells were replaced by solid cords. Preparations for neutral fat, stained with pyridine-oil red O and hematoxylin, revealed no lipoid substance in the cytoplasm. Many of the compressed nerve roots, however, showed fatty metamorphosis of the myelin, and the spinal cord revealed the fatty metamorphosis of primary and secondary degeneration of central nerve fibers. At the site of greatest compression of the spinal cord, the architecture was greatly altered, the blood vessels were thickened, swarms of fat-filled macrophages replaced the white columns and the bodies of the nerve cells revealed profound regressive changes (figure 3). In the lumbosacral region, the architectonics were intact, but the anterior motor horn cells revealed a variety of regressive changes which varied from acute axonal reaction to vacuolization, diffuse chromatolysis and chronic atrophy. Many ghost cells could be seen scattered throughout. In the cervicothoracic region, the tumor invaded the dentate ligaments and extended into the dura mater spinalis. Here the blood vessels and sheets of endothelial cells provoked a marked connective tissue reaction. Perdrau preparations very clearly delineated the vascular component of the tumor while the sheets of endothelial cells were completely devoid of reticulin fibrils.

DISCUSSION

The pathologic picture was that of a diffuse hemangio-endothelioma with foci of multicentric origin in the spinal and cerebral leptomeninges and in the cores of the choroid plexuses of the lateral and third ventricles. This tumor was histologically benign and, although it had spread throughout the spinal subarachnoid space, at no point did it penetrate the pia-glial membrane. It invaded the spinal dura mater by extension into the dentate ligaments and provoked a marked connective tissue reaction in both the pia and dura mater. At the base of the brain, the tumor mass was sharply delineated from the cerebral sub-

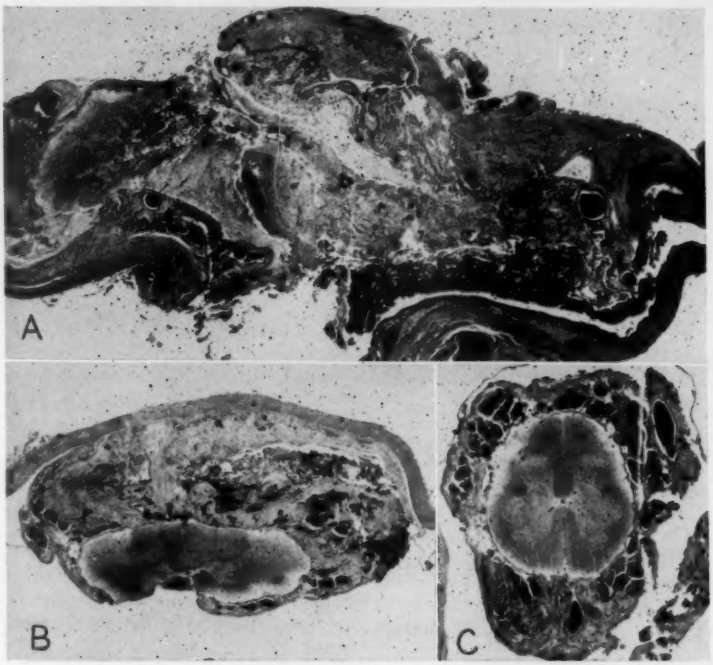


FIG. 3. Transverse section of the spinal cord showing in (A) the destruction of the cervicothoracic level and invasion of the dura mater; (B) large tumor mass in the subarachnoid space at a high thoracic level; and in (C) tumor about the nerve roots at a lumbar level. Weil-van Gieson stain.

stance but in the lateral and third ventricles there was local extension from the cores of the choroid plexuses, which were completely replaced by neoplasm, into the paraventricular brain substance. At no site did the tumor have the appearance of an angiosarcoma. The histological picture of sheets of tumor cells originating from solid buds coming from blood vessels differentiated this hemangioendothelioma from a diffuse endothelioma or mesothelioma of the leptomeninx with secondary vascularization. The increased intracranial pressure apparently resulted from obstruction of the cerebral subarachnoid spaces in the vicinity of the ambient cistern, and the transverse myelopathy resulted from local compression of the spinal cord by the diffuse leptomeningeal hemangio - endothelioma and interference with the arterial supply and venous drainage.

Although there was an unverified history of cystic disease of the kidneys in the mother and in four others on the maternal side of the family, the tumor did not have the appearance of a hemangioblastoma which is the basic lesion in Lindau's disease. No evidence of cysts were found in the kidneys or in the pancreas. It is becoming more and more evident that, al-

though von Hippel-Lindau disease is a distinct clinical pathologic entity, it belongs to a larger family of angiomatous disorders in which a variety of vascular changes occur. The association of cystic disease of the kidneys with aneurysms of the circle of Willis probably represents another component of this family of disorders. Whether or not the diffuse hemangioendothelioma in this case is a congenital disorder or is a manifestation of a basic familial taint cannot be decided with certainty. In the realm of vascular neoplasms, it may be exceedingly difficult at times to differentiate a malformation which develops into a true tumor from a tumor arising without any previous anatomical abnormality. Although some may object to the statement that this tumor is histologically benign despite its invasion in the subependymal region of the brain, we cannot use the designation of angiosarcoma or hemangio-endothelial sarcoma, for such designations are reserved for tumors of wholly different histologic structure.

The external surface of the brain is convoluted or furrowed—that is, numerous clefts and divisions cut up apparently the outer portion of the brain into many irregular parts called convolutions. These convolutions covered by a thin membrane and net-work of blood-vessels, are all that we see on looking at the brain when the head is opened by removing the superior part of the skull, or when the brain is removed from the skull and placed on its base before us. On reversing the brain and looking at its base, or the under side of this organ we observe a very different aspect. We notice great irregularity produced by the form of the skull and which gives occasion to divide the brain into an anterior, middle and posterior portion. We also now see the union of the greater and the lesser brain and their connection with the spinal marrow. The upper portion of the spinal marrow, or that which lies within the cranium, is seen much enlarged, and is called the medulla oblongata. At the upper part of the medulla oblongata is seen a large, thick, white band, nearly an inch in width, called the pons Varolii, and which unites the two portions of the cerebellum.

Above this band we also see two rounded fibrous bodies coming through the pons Varolii and diverging from each other into the hemispheres of the cerebrum. These are called the crura cerebri.

—Amariah Brigham in *An Inquiry concerning the Diseases and Functions of the Brain, the Spinal Cord and the Nerves*, published in 1840.

NEWSLETTER

SEPTEMBER-OCTOBER, 1951

Pearce Bailey, President
Howard D. Fabing, President-Elect
Walter O. Klingman, Vice-President
Francis M. Forster, Secretary
Joe R. Brown, Treasurer

AMERICAN ACADEMY OF NEUROLOGY

AAN Review Courses Now Organized Plans for intensive review courses in neuropathology, neuroroentgenology and electroencephalography to precede the Academy meeting in Louisville (April 24-25, 1952) have crystallized. The two day course in neuropathology (April 22 and 23) will follow the design of the previous course given at Virginia Beach this year. Material to be covered includes staining techniques, cytology, normal structure and pathologic alterations in neurologic disorders. Clinical correlations will be emphasized. Evening hours will be used for reviewing slides with a projectoscope. Two months prior to the session each registrant for the course will receive a loan collection of 100 microscopic slides for advance study. Also, each registrant will be permitted to keep his loan set for one month after the course for additional review. Enrollment is limited to 50 applicants. The fee for the neuropathology course is $25.00 for junior members, $50.00 for senior members and $100.00 for non-members. A $25.00 deposit fee for the loan box of slides is required....A one day course in neuroroentgenology, under the direction of Dr. Harold Peterson, professor of neuroroentgenology at the University of Minnesota, will be held April 22. This course will present a comprehensive review of neuroroentgenology including encephalography, angiography and myelography. These presentations will be preceded by background neuroanatomical demonstrations by Dr. A. R. Vonderahe of the University of Cincinnati. The course is limited to 50 applicants. The fee for the course is $15.00 for junior members, $30.00 for fellows and active members and $50.00 for non-members....A one day intensive EEG course will be given April 23. This course is designed to give practicing physicians a basic orientation and workable knowledge in the field of electroencephalography. It is not intended to develop experts. Rather, it is slanted from a practical viewpoint to succinctly delineate the ABC's of EEG interpretations and their clinical significance. The course is limited to 40 applicants. The fee for the course is the same as that for neuroroentgenology.... Applications for all these courses are now being accepted and should be forwarded to Dr. A. B. Baker, Chairman, Committee on Education, 19 Millard Hall, University of Minnesota, Minneapolis 14. Priority will be determined by the date of application.

ANA and Section of AMA Elect New Officers At its 76th annual meeting (June 18-20) the American Neurological Association elected the following officers for the year 1951 to 1952: S. Bernard Wortis, pres.; Hans H. Reese, pres.-elect; Frederick P. Moersch, first vice pres.; A. Earl Walker, second vice pres. H. Houston Merritt and Charles Rupp

continue as secretary-treas. and assistant secretary, respectively. Charles D. Aring was elected to the council to succeed John Romano, whose term expired....At the meeting of the Section on Mental and Nervous Diseases of the AMA (June 14-16) in Atlantic City, Frank Luton was elected chairman; A. Earl Walker, vice chairman; and Francis J. Gerty, representative of the Section to the American Board of P & N. Francis M. Forster continues as secretary; Hans Reese is delegate to the House of Delegates of the AMA; Paul Bucy is alternate delegate, and Leon Whitsell is chairman of the scientific exhibits....At the section meeting a resolution was passed requesting the admission of civilian paraplegic patients to VA paraplegic centers. Also, a committee on the problems of licensure and certification of clinical psychologists was organized to work in conjunction with the Bureau of Legal Medicine. The chairman's address by Louis Karnosh was on neurology and human emotions.

Gordon Holmes Compliments Editors of NEUROLOGY R. Wartenberg reports receiving a message from Dr. Gordon Holmes, part of which is as follows: "I have received the copy of NEUROLOGY which you kindly sent me. I was very interested in reading it through, and congratulate you and your fellow editors in producing such a valuable and discriminately edited and reproduced number."

* * * * * *

Expansion of Neurology Predicted for Los Angeles The opening of U.C.L.A.'s new School of Medicine this fall promises to add another good training center for neurology on the West Coast. Although construction of the medical school buildings and university hospital is not expected to be under way before September, adequate clinical facilities are assured through the school's affiliation with the Veterans Hospital and Center which stands within a few blocks of the U.C.L.A. campus. The neurology service at the Veterans Center is accredited for residency training in neurology and consists of an acute neurologic ward of 31 beds, 60 neurologic beds on the general medical service, a domiciliary unit for 450 patients with chronic neurologic disease, and a special epilepsy project. A rapid turnover of patients is maintained on the neurologic ward, while the domiciliary unit provides a unique opportunity for the study of chronic neurology. Plans for full development of these facilities for teaching and research in conjunction with the U.C.L.A. School of Medicine are now being implemented by Augustus S. Rose, professor of neurology at U.C.L.A., and Ralph W. Barris, chief of neurology at the Veterans Center....Neurology at U.C.L.A. is a division of the department of medicine and is expected to remain so until after the University Hospital has increased its bed capacity over the presently planned 250. The California Department of Mental Hygiene is now drawing plans for the construction of a 400-bed hospital to be placed on the university campus adjacent to the general hospital, and one-fourth of these beds will be allocated to physical disease of the nervous system....

Neurology at Albany Returns to Independent Status The Board of Trustees of the Albany Medical College and Hospital have voted to separate the department of neurology from the department of psychiatry and return it to its status as an independent department. Robert W. Graves is chairman of the new department and neurologist-in-chief to the hospital. He is assisted by Frederick Hesser, former assistant professor of neurology at the State University of Iowa College of Medicine, who joined the Albany staff on May 15th.

Charles K. Mills Neurology Building To Open in Philadelphia A new modern buff brick structure now looms impressively on the grounds of the Philadelphia General Hospital. Dedicated to the memory of Charles K. Mills (1845-1931), noted Philadelphia neurologist, this ultramodern building of seven stories will supersede the present men's and women's nervous buildings of the Philadelphia General Hospital. Containing approximately 725 beds for neurologic patients, two large amphitheatres, numerous small class rooms and out-patient clinics, the building will serve as a teaching center for all of the Philadelphia medical schools. Dedicatory exercises are planned for September 25, 1951. Two full-time positions for clinical director are now available. Communications should be sent to Dr. P. F. Lucchesi, Medical Director, Philadelphia General Hospital, Philadelphia 4, Pa.

* * * * * *

American Board of P & N Establishes Policy for Accrediting Active Military Duty David A. Boyd, Jr., acting secretary-treasurer of the American Board of Psychiatry and Neurology, announces that the Board has established a policy for accrediting training and experience for physicians on active military medical duty since July 1, 1950. One year of training credit will be granted for one year spent in full-time psychiatric and/or neurological duties. Additional training credit will be given for that amount of time spent in approved training programs. Experience credit will be granted for any remaining time spent in full-time psychiatric and/or neurological assignments. Double credit will not be granted for any single period of time....At the Board examinations held in Philadelphia (June 11 and 12) the following candidates were certified in neurology: Maurice J. Barry, Jr. (supplementary certification), Carl Blackstone Booth, John Campbell, Sidney Maximilian Cohen, Irving S. Cooper, David deR. Daly, Carl J. Graf, B. Marvin Hand, Christopher A. Iannucci, Sherman Eli Kaplitz, Robert E. Litman, Peter Paul Machung, Arthur M. Schwartz, Steven D. Schwartz, John W. Sumner, Jr., Fae Y. Tichy, Dewey Kiper Ziegler, and Eli Robins (certified in both neurology and psychiatry).

ANA Transactions Available by Purchase H. Houston Merritt, ANA secretary, announces that the Transactions of the American Neurological Association, which contain abstracts of papers and demonstrations presented at each annual

meeting, may be purchased at $3.50 per copy (plus postage, and plus sales tax for New York City). Orders should be forwarded to Dr. Merritt, 710 West 168th Street, New York 32, New York.

Cerebral Palsy Group Holds First Symposium The United Cerebral Palsy Associations, Inc. held its first symposium at the Academy of Medicine in New York City, April 14. Doctors Wilder Penfield and Sidney Farber served as chairmen of the meeting. Among those participating in the program were Doctors Abner Wolf, H. W. Magoun, Seymour Kety, Klaus H. Unna, Bronson Crothers, Russel Meyers and H. Houston Merritt. The United Cerebral Palsy Association was established in 1949 to promote research along broad lines and to provide scholarships and endowments for the care, education and employment of the palsied. The address of the Association is 50 West 57th Street, New York 19, New York. The executive director is Karl K. Van Meter.

Briefs A neurovegetativen symposium will be held in Uberling (Bodensee), September 15-16, 1951. The theme of the symposium is "Der periphere neurovegative Vorgang." The chairman is Prof. Dr. A. Sturm, Heusnerstr. 29, Wuppertal-Barman, Germany....A bill has been passed appropriating $1,187,400 for the forthcoming year, to implement the newly established Institute of Neurological Diseases and Blindness as one of the National Institutes of Public Health....L. E. Daniels, professor of neurology, University of Colorado School of Medicine, is formulating plans for a neurology residency training program in affiliation with the new Denver veterans hospital which is adjacent to the medical school grounds. Milton G. Shy, trained at Queen Square and Montreal, is the new associate professor at the Colorado school....Howard V. Petzold is now chief of the neurology section at the veterans hospital in San Francisco....William K. Jordan has deserted Seattle to become professor of neurology at the University of Arkansas School of Medicine....The central neuropsychiatric association will meet in Minneapolis October 19 & 20 at Hotel Nicollet. The Minnesota Society of Neurology and Psychiatry are hosts to the association....

Percy Bailey

Neurology

.....BOOK REVIEWS....

Progress in Neurology and Psychiatry

An Annual Review, Volume 5. E. A. Spiegel, M.D., Editor. 1950. New York: Grune and Stratton, 621 pages.

The fifth volume of *Progress in Neurology and Psychiatry*, edited by Dr. E. A. Spiegel, is another important contribution to current neurologic literature. With his corps of excellent co-editors, Dr. Spiegel has summarized the important contributions for the year 1949 in neuroanatomy, neurophysiology, neuropathology, neuropharmacology, clinical neurology, neurosurgery and psychiatry. It is not possible to review individually the various subjects and the contributions of the editors in the subdivisions, but it should be said that the Spiegel volumes on *Progress in Neurology and Psychiatry* have become handbooks of current medical advancement and reference sources in which one can seek information regarding every current subject within the field. The only possible criticism of the book is that the general index is too brief. If it were somewhat more complete, although to make it so would be time-consuming effort, the volume would give additional help to the neurologist.

R. N. DeJ.

Cranioplasty

David L. Reeves, M.D. 1951. Publication Number 39, American Lecture Series. Springfield, Illinois: Charles C Thomas, Publisher. 119 pages, $3.00.

This little book is a well written account of the development of cranioplasty and an explicit description of the author's experience with the technique in Army general hospitals during World War II.

The history of cranioplasty probably dates to the beginning of surgical practices, for one of the earliest techniques attempted by primitive man was trephination. But the practice apparently never became generally accepted, as the skepticism of the Renaissance surgeons indicates, until the modern era. Within the last half century most of the present day cranioplastic procedures have been introduced. The various techniques of autogenous grafting are presented in the monograph as they were developed. Homogenous and heterogenous grafts are dismissed as impractical at this time. Alloplastic grafts, which the author stresses, although used in the

early part of the century, came into popularity about the time of World War II. The descriptions of the techniques of tantalum and acrylic cranioplasty are given in such detail that a novice could carry out the procedure by following directions.

The indications for cranioplasty follow current teachings. The author stresses the need for complete wound healing before a plate is inserted into a cranial defect, stating that in the presence of infection, scattered successes with cranioplasty do not justify the procedure.

Perhaps the most interesting part of the monograph is the author's discussion of his personal series of 196 cases of cranioplasty. By means of numerous illustrations and a number of case reports the various types of cranial defect and their repair is present in detail.

A fairly complete and accurate bibliography on the subject is appended. The numerous illustrations are well chosen and clear. The pleasing format of the book and the author's free style make the text easy to read.

This lecture, a welcome addition to the neurosurgeon's library, should be a valuable reference book to everyone interested in cranial surgery.

A. E. W.

Speech Habilitation in Cerebral Palsy

Marion T. Cass. 1951. New York: Columbia University Press, 212 pages, $3.00.

The chief value of this book lies in the thorough exposition of techniques for the actual teaching of phonetic sounds. The author systematically goes through 34 phonetic sounds giving detailed instructions and exercises. There is also a section on the general methodology of relaxation with instructions for passive, passive-assisted and active exercise of the muscles involved in speech. A valuable appendix reviews the muscles involved in articulation, volcalization and the respiratory aspects of speech.

Dr. Cass, an instructor in speech science, stresses the fact that speech training in the cerebral palsied requires not only teaching unlearned sounds but also altering faulty motor patterns and establishing correct patterns in their place. Mention is made of the possibility of shifting cerebral dominance. This is a concept which represents a certain amount of wishful thinking rather than actual scientific fact. There is perhaps not enough recognition of the influence of general intellectual factors in this discussion of speech retraining. The early chapters on neuroanatomy and neurophysiology are elementary and the weakest part of the book.

The final chapter, entitled "Educational Problems," will repay the attention of anyone interested in any aspect of management and treatment of cerebral palsy. The principles laid down for the establishment and maintenance of special classes are general but perfectly valid for all phases of the habilitation and rehabilitation of the brain injured child. This section of the book alone makes Dr. Cass's effort a valuable contribution to the theory of the education, treatment and management of disabled individuals.

A. L. D.

Complete Epileptic Seizure-control; First Step in Rehabilitation

In the drug therapy of the epileptic, nothing short of *complete* suppression of seizures can rightly be called full success. Complete seizure-control is a prerequisite to the patient's return to a normally active life. Carter[1] states: "Basically all efforts should be directed toward preventing seizures and the tendency to chronic invalidism."

The management regimen should include:[1]

I. Good physical and mental hygiene.
   a) Wholesome diet; Regular bowel habits; Avoid noxious materials, e.g. alcoholics; Moderate physical activity.
   b) Help overcome feeling that epilepsy is shameful; Encourage normal work and recreation; Regular sleep without overprotection.

II. Anticonvulsant medication selected on the basis of Exact Diagnosis:
   "Certain drugs are more effective in one type of seizure than they are in another, and it is necessary to use proper drugs. The dosage must be individualized for each case."[1]

Thus, the best guide in selecting medication for a patient is the type of seizures present. (Frequently several drugs in combination is most effective.)

The table shows which drugs are indicated for each type of seizure. It will be noted that the newer hydantoin, Mesantoin, is effective for *grand mal*, Jacksonian and focal seizures.

MESANTOIN DOSAGE is adjusted to the lowest level adequate to attain freedom from seizures. Start with ½ or 1 tablet daily during the first week; increase the daily intake by ½ or 1 tablet during the next week. Continue this up to optimal dosage. When another drug has not given good results, Mesantoin is added by the same procedure; then the old drug is gradually reduced.

SIDE EFFECTS — Mesantoin produces side effects in some cases: Skin and blood changes are signs of sensitivity — the drug should be discontinued. Drowsiness develops upon reaching maximum dosage.

PRECAUTIONS — Certain precautions are necessary to minimize untoward effects.
   a. close check on patient — repeated visits and blood counts.
   b. No Mesantoin, if white cell count below 4000.
   c. caution if (1) rash or blood changes.
      (2) History of drug sensitivity.
   d. discontinue drug if (1) bleeding of gums or vagina.
      (2) Sore throat

TYPE OF EPILEPSY	PRIMARY CLINICAL MANIFESTATIONS	MEDICATION	AVERAGE ADULT DAILY DOSE★	LIMITING SIDE EFFECTS	SIGNS OF SENSITIVITY
GRAND MAL	Aura followed by loss of consciousness; tonic-clonic convulsions and autonomic disturbance, e.g., in bladder function.	Phenobarbital	1¼ grs. h.s. Usual max.: 3 grs. per day	Sleepiness	
		5,5 diphenyl hydantoin	1½ grs. t.i.d., p.c. Usual max. 6 grs. per day	Diplopia, staggering (may increase petit mal)	Overgrowth of gums, body hairs; itching rash on extremities, gastric irritation
JACKSONIAN	Convulsions begin in one area and spread outwards (Jacksonian march.). No loss of consciousness.[3]	3 methyl 5,5 phenylethyl hydantoin (mesantoin)	Adults: 2 to 6 tabs. Children: 1 to 4 tabs.	Sleepiness	Full details given; see Psychomotor cross-column below
		phenylacetylurea[3]	2 Gms. per day. Max. dose 6 Gms. per day[4]	Drowsiness[5]	Central nervous system affected, nausea, vomiting and abdominal pain[5]
PSYCHO MOTOR	Period of amnesia; actions apparently purposeful but mechanical; incoordination. Mild tonic spasms. In children: "behavior problems".[3]	3 methyl 5,5 phenylethyl hydantoin[4]	Adults: 2-6 tabs. Children: 1-4 tabs.	Pharyngitis, mucous membrane bleeding, lymphadenopathy, measles-like rash with itching and fever; in severe reaction: blood dyscrasia.	
		phenylacetylurea[3]	See phenylacetylurea—above		
PETIT MAL TRIAD	Attacks: in series (rapid succession), abrupt onset, few sec. duration; no aura nor impairment of consciousness. Rhythmic twitching (e.g. eyelids).	3,5,5 trimethyl oxazolidine 2,4 dione	0.9 to 1.2 Gms.	Inability to see in a bright light. Drowsiness	Hiccough, acneform rash, leukopenia
		N methyl derivative of phenobarbital	6 grs.	Sleepiness	

★Although an average daily dose can be stated for each of these drugs, to obtain best results it is necessary that the physician determine the dose required by each individual patient for maximum control of his seizures.

Bibliography: 1. Carter, S., in Conn, H.: Current Therapy 1949; Phila., Saunders Co., p. 495. 2. Kaufman, I.: Dis. Nerv. System *11:* 99, 1950. 3. Lennox W.: Science & Seizures, ed. 2, N.Y.C., Harper & Bros., 1946. 4. Harris, T. & Otto, J.: Texas J. Med. *43:* 328, 1947. 5. Little S. & McBryde, R.: Am. J. M. Sc. *219:* 494, 1950. (Except as otherwise indicated, the data tabulated is from: Gibbs, F.: Ann. Int. Med. *27:* 548, 1947.)

Sandoz Pharmaceuticals
DIVISION OF SANDOZ CHEMICAL WORKS, INC.
68 CHARLTON STREET, NEW YORK 14, N. Y.

CEREBRAL PALSY INSTITUTE

January 21 - February 1, 1952

and

THREE MONTH POST-GRADUATE COURSE FOR PHYSICIANS

February 4 - April 25, 1952

SPONSORED BY

The Coordinating Council for Cerebral Palsy in New York City, Inc.

IN COOPERATION WITH

College of Physicians and Surgeons, Columbia University, and the various diagnostic and treatment centers of Greater New York

A limited number of Study Fellowships are available

FOR FULL INFORMATION, WRITE:

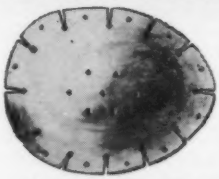
Miss Marguerite Abbott, Executive Director
The Coordinating Council for Cerebral Palsy in New York City, Inc.
270 Park Avenue, New York 17, N. Y.

When replacing a cranium piece

SAVE TIME

with Nudell's Universal

TEMPLATES



IN 8 ASSORTED SIZES

Employed by many neuro-surgeons these templates reduce the time of operation. Available in stainless steel or tantalum in varying degrees of curvature. Slots cut on the periphery facilitate final shaping while perforations permit fluid escape and growth of granulation tissue.

DEPTH CHECK DRILL. This drill fits the Hudson Brace and permits an accurate, predetermined depth of skull penetration. In stainless steel.

Write Dept. N for literature and price list.

UZA NUDELL

Technician to Neuro-Surgeons

125 WEST 45TH ST. NEW YORK 19, N.Y.

new dosage form

for the bag

Dilaudid* sulfate

10 cc. Multiple Dose Vial

Each cc. contains 2 mg. (1/32 gr.) dihydromorphinone (Dilaudid) sulfate in sterile solution—convenient and ready for instant use.

Dilaudid—a powerful analgesic—dose, 1/32 grain to 1/20 grain.
a potent cough sedative—dose, 1/128 grain to 1/64 grain.
an opiate, may be habit forming.

*Dilaudid is subject to Federal narcotic regulations.
*Dilaudid®, E. Bilhuber, Inc.

BILHUBER-KNOLL CORP. ORANGE, NEW JERSEY, U. S. A.

All your books in Neurology and Psychiatry

from one source

We have a complete stock, including imported and hard-to-get books. We locate out-of-print books.

Ask for our Bibliography and Neurology list.

Write for a description of a new, dissectible brain model.

ROBERT BRUNNER 1210 Avenue of the Americas NEW YORK 19, N. Y.

FOR SAFE SEDATION
Without Risk of Habituation

TO ALLAY ANXIETY
Without Penalty

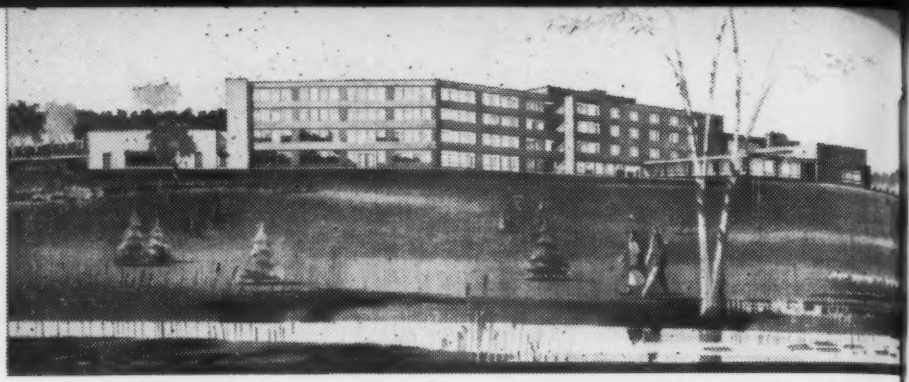
Prescribe

PASADYNE (Daniel)

Sedative - Hypnotic
Antispasmodic

NO SEQUELAE FOLLOWS ITS USE
A Strictly Ethical Preparation for Professional use only.
Clinical Samples and Literature on request

JOHN B. DANIEL, INC. ATLANTA, GEORGIA



Hospital's new wing: front elevation

FOR YOUR NEUROLOGIC PATIENTS: A NEW SERVICE *in the Northwest*

CONGRATULATIONS continue to pour in on developments in our quarter million dollar neurology unit. It is a resource overwhelmingly accepted and appreciated by the physicians of the upper midwest. The completeness of the plant and its facilities, the beauty of the location of this large tract of land adjoining Minneapolis—park and lakes on highways leading to the north and west—has aroused the enthusiasm of those who have made an inspection. Besides these there are many other great advantages.

These are: well equipped training, rehabilitation and gymnasium premises, clublike recreation rooms, a self-service laundry, beauty parlor, game rooms, record rooms, laboratory. Electroencephalographic service and an aphasia clinic (one of the few in the United States) are of very special significance. The imaginative understanding of the staff meets with response on the part of the patients who soon begin to wait on themselves and there is a very happy spirit prevailing in the entire establishment.

This is the first non-governmental hospital in the northwest for retraining patients with neurological disabilities. The center has full and elaborate facilities for 1) treatment of the hemiplegic patient, 2) multiple sclerosis, 3) retraining of speech disorders, 4) paraplegia and other paralyses, 5) ataxias.

Those of you who have not taken the opportunity to visit this hospital and center are invited to do so when in Minneapolis. You will see that treatment of patients definitely is not a policy of mere bed accommodation but a program of care which can be carried out only with staff and equipment such as is available here.

Care here finds its main center of expression in a helpful environment. Beautiful surroundings are a contributing factor and the policy that prevails in a voluntary, nonprofit neuropsychiatric hospital is immediately recognizable and appreciated as being incalculably valuable.

Write for free booklet.

Glenwood Hills Hospitals

ADJOINING GLENWOOD PARK AND TWIN LAKES

OPERATED IN CONNECTION WITH HOMEWOOD HOSPITAL PLYMOUTH AT PENN

3901 GOLDEN VALLEY RD. MINNEAPOLIS 22, MINN.

BALDPATE, Inc.

Georgetown, Massachusetts

Located in the hills of Essex County, thirty miles north of Boston.

For the treatment of neuroses, personality disorders, psychoses, alcoholism and drug addiction.

Psychotherapy is the basis of treatment; other methods such as shock therapy, malaria and fever box are used when indicated.

Occupational therapy, outdoor activities, picnics and other diversions.

GEORGE M. SCHLOMER, M.D., Medical Director

FOUNDED 1879

RING SANATORIUM

Eight miles from Boston at an elevation of 400 feet

For the study, care and treatment of emotional, mental, personality, and habit disorders.

All recognized psychiatric therapies are used as indicated.

Cottage accommodations meet varied individual needs. Limited facilities for the continued care of progressive disorders requiring medical, psychiatric, or neurological supervision.

Director: **Benjamin Simon, M.D.**
Associates: **Charles E. White, M.D.**
Louis Brenner, M.D.
William R. Shelton, M.D.

Consultants in All Specialties

Arlington Heights, Massachusetts
Telephone AR 5-0081

Francis W. Russell
Executive Secretary

The Ann Arbor School

for children with educational, emotional or speech problems

The school programs are directed by an excellent staff of teachers in special education; a speech therapist, recreational and occupational therapists and a clinical psychologist.

A training center in special education for student teachers at the University of Michigan.

Complete reports sent to referring physicians at end of each term. Licensed by the Department of Public Instruction.

Registered by the A.M.A. Member American Hospital Association.

For catalog and information address

THE REGISTRAR
1700 Broadway, Ann Arbor, Michigan

Announcing the New

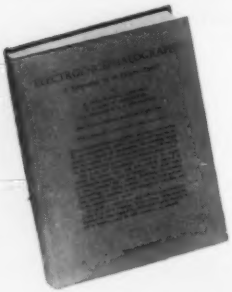
The Electrical Activity of the Nervous System

by Mary Brazier

THIS book by Mary Brazier, Neurophysiologist, Massachusetts General Hospital and Research Associate, Harvard Medical School, is the first book to bring together under one cover the present knowledge of the electrical activity of the nervous system.

This work will be found indispensable not only by all physiology and medical students, but also by neurophysiologists and research workers in electrophysiology, and all those responsible for teaching these subjects in colleges and medical schools. Profusely illustrated.

$5.00

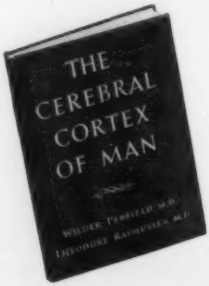


ELECTROENCEPHALOGRAPHY

by Hill-Parr

The first comprehensive textbook on electroencephalography.

$13.00



A summary of present-day knowledge of the cerebral cortex and its function.

$6.50

The Macmillan Company
60 Fifth Avenue, New York 11

Please send me the books checked below. I will either remit in full or return the books in ten days.

☐ Brazier: THE ELECTRICAL ACTIVITY OF THE NERVOUS SYSTEM
☐ Hill-Parr: ELECTROENCEPHALOGRAPHY ☐ Penfield-Rasmussen: THE CEREBRAL CORTEX OF MAN

Name .....

Address .....

macmillan

"bloating, belching and indigestion"

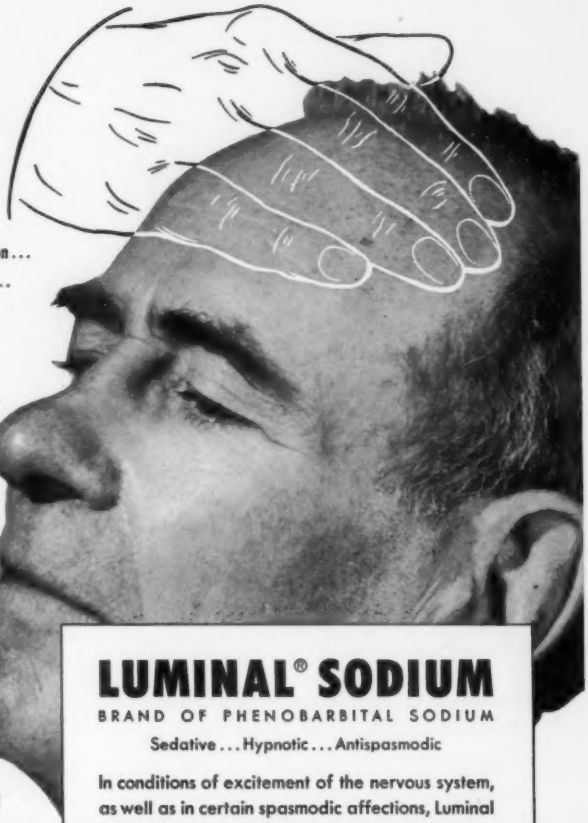
You can provide extraordinary relief of the bloating, belching and other complaints of many of your patients with so-called functional indigestion by prescribing Bilogen — a therapeutically designed choleretic-digestant. In each Bilogen tablet you'll find: Ox bile extract (2 grs.) to stimulate bile secretion, oxidized mixed ox bile acids (1¼ grs.) to flush biliary ducts, desoxycholic acid (½ gr.) to promote fat absorption, and a pancreatin of high digestive power (equivalent to 3¾ grs. Pancreatin, U. S. P.) to exert enzymatic action. Note too that this pancreatin is given double protection with a special coating to insure its release in the intestine. The coordinated action of the four Bilogen ingredients provides natural biliary stimulation, relieves upper abdominal distress, and re-establishes normal functions. Bilogen is available in bottles of 100 and 1000 tablets.

Organon INC. • ORANGE, N. J.

BILOGEN®

Organon

the quieting hand



—in preoperative apprehension...
postoperative restlessness...
insomnia...
epilepsy...
dysmenorrhea...
vomiting of pregnancy...
eclampsia...
hypertension...
pyloric spasm...
neuroses...

NEW, EASILY OPENED SERRATED AMPUL

—Luminal Sodium Powder is available in a new, constricted-neck ampul—serrated for easy opening. Only moderate pressure is required to make the file cut.

LUMINAL® SODIUM

BRAND OF PHENOBARBITAL SODIUM

Sedative...Hypnotic...Antispasmodic

In conditions of excitement of the nervous system, as well as in certain spasmodic affections, Luminal Sodium acts as a soothing, quieting agent to tranquilize hyperexcitability or to curb convulsive paroxysms. Small doses have a pronounced sedative and antispasmodic action. Large doses are markedly hypnotic.

For oral use... tablets of 16 mg. (¼ grain), 32 mg. (½ grain) and 0.1 Gm. (1½ grains).

For parenteral use... solution in propylene glycol 0.32 Gm. (5 grains) in 2 cc. ampuls; powder 0.13 and 0.32 Gm. (2 and 5 grains) in ampuls.

Winthrop-Stearns INC.
NEW YORK, N. Y. WINDSOR, ONT.

Luminal, trademark reg. U. S. & Canada